Division of

Cancer Prevention and Control

1986 Annual Report

October 1, 1985-
September 30, 1986

U.S. DEPARTMENT
OF HEALTH
AND HUMAN SERVICES

National
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Director's Report

This report describes the intramural research program of the Division of Cancer Prevention and Control (DCPC), one of the four major program divisions of the National Cancer Institute. The DCPC has the responsibility for all cancer control research and related program activities under the National Cancer Plan, as well as research to develop, refine and validate methods of cancer prevention. The overall cancer prevention and control program has changed significantly over the past several years, with renewed emphasis on scientific validation of the methods to control cancer, development of programs to stimulate the involvement of communities and organizations in cancer control, efforts to expand our current knowledge of cancer prevention and validate methods to reduce the incidence of cancer, and surveillance programs to track progress and problems in cancer.

ORGANIZATION

Figure 1 outlines the DCPC organization. The Division consists of three major programs, each led by an Associate Director. The Office of the Division Director provides overall coordination and direction and analytic program support. Each program is described briefly below.

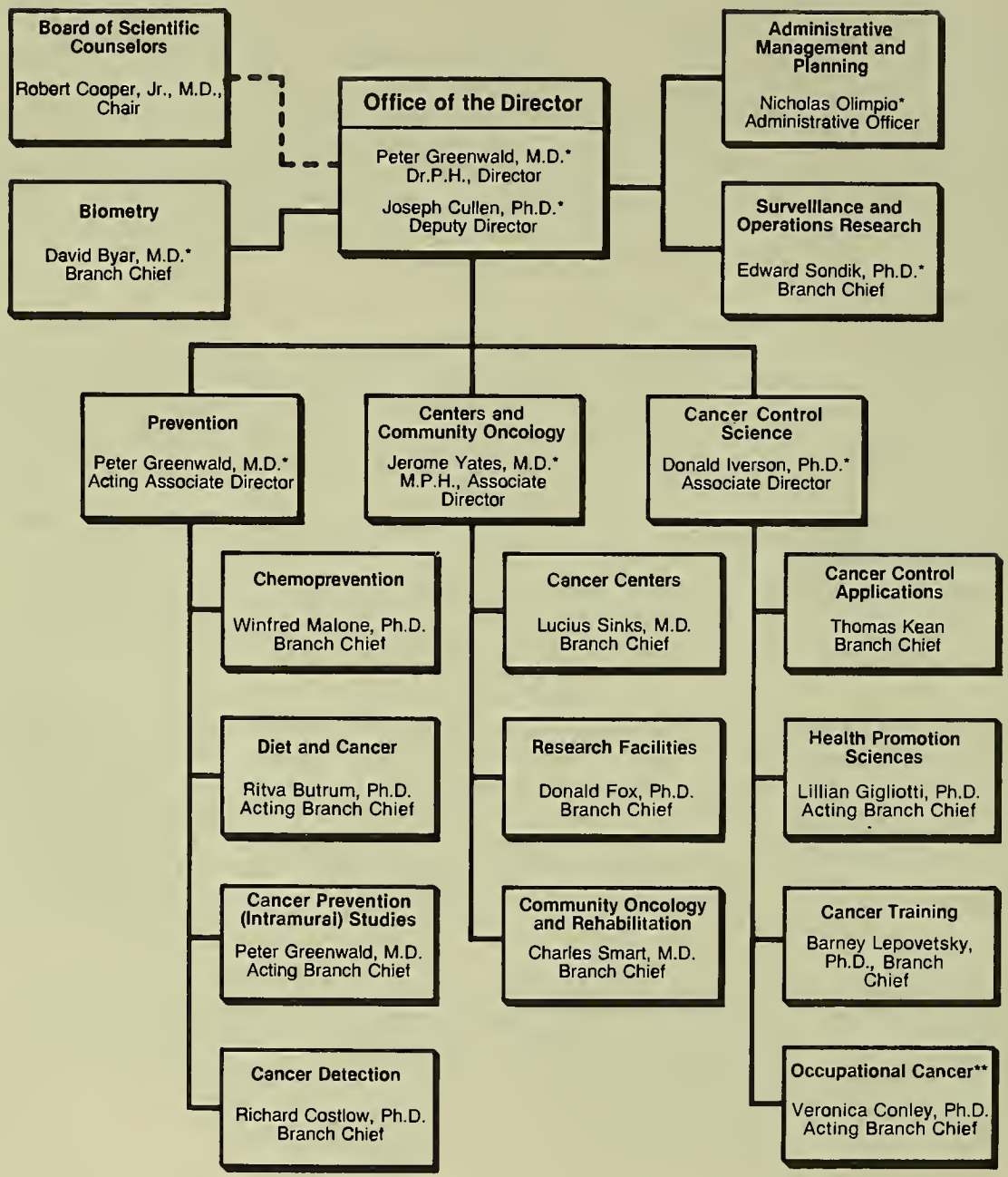
The Prevention Program is charged with planning and supporting both intramural and extramural research in chemoprevention, diet and cancer, and cancer detection. In addition, this organizational unit serves as the focal point for coordinating diet, nutrition, and cancer activities across the NCI divisions. This program houses the Cancer Prevention Studies Branch, one of two intramural branches.

The Centers and Community Oncology (CCO) Program supports shared research resources in cancer centers and applied research resources in the delivery of treatment, continuing care, and rehabilitation of patients with cancer. Within the Division of Cancer Prevention and Control, the CCO Program provides the framework for the integration of cancer centers and community activities. The CCO Program also has the responsibility of stimulating, developing, applying, and disseminating knowledge and technology related to cancer patient management.

The Cancer Control Science Program supports an integrated approach to cancer control research and applications. Program efforts are directed toward establishing cancer control as a scientific program where research on intervention strategies and their impact on populations is given primary attention.

FIGURE 1

Division of Cancer Prevention and Control Organization Chart



* Members of DCPC Director's Committee
** Transfer from Prevention Pending Approval

The Office of the Director is responsible for the coordination and direction of the Division programs. It includes three branches: the Surveillance and Operations Research Branch, the Biometry Branch (an intramural branch), and the Administrative Management and Planning Branch. The Surveillance and Operations Research Branch includes the Surveillance, Epidemiology, and End Results (SEER) program and supports the Division in operations research, epidemiology, program evaluation, and computer technology. The Biometry Branch supports research using SEER and other epidemiological data bases, research in biostatistical methodology, and clinical trials research. The Administrative Management and Planning Branch assists in the management of the Division's budget and administrative matters. The Office of the Director is also responsible for coordinating the NCI-wide Smoking, Tobacco, and Cancer Program.

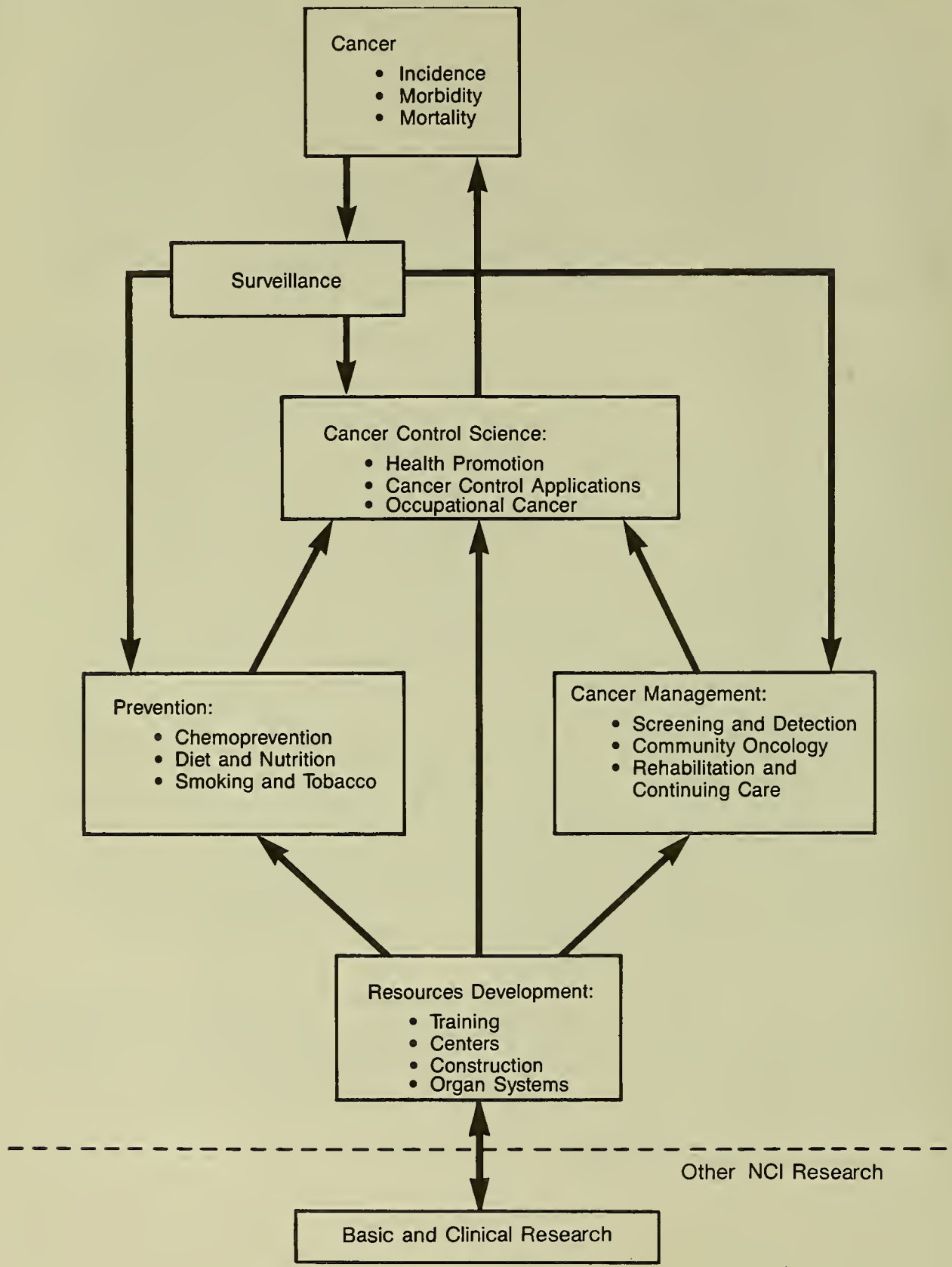
From a cancer control perspective, the Division's interrelated programs can be grouped into five activity areas (Figure 2). First are the Prevention Program components that are directed toward reducing cancer incidence: chemoprevention, diet and nutrition, and smoking and tobacco. Second are components aimed at research to reduce morbidity and increase survival. These cancer care and management-oriented activities include screening and detection, and community oncology which includes rehabilitation and continuing care. These prevention and cancer care research components are supported by the Cancer Control Surveillance and the Resources Development activities. Lastly, to translate into practical applications the knowledge learned from research in the prevention and cancer care components, the Cancer Control Science component conducts research in technology transfer, health promotion, and occupational cancer so that the public will benefit either directly or through the health system.

Intramural research is an important component of the programs of the Division of Cancer Prevention and Control. The presence of an intramural program provides extramural program directors ready access to technical expertise relevant to scientific and management decisions. Moreover, an intramural program brings to the Division the resources to take advantage of a number of research and cancer control opportunities unique to, or important to, the Federal Government including international or interagency collaborations and rapid access to specific high risk target populations. The program also enables methodological research to be persued that is fundamental to developing the technical approach underlying many large-scale cancer control research projects.

Within DCPC, the intramural research program is conducted through the Cancer Prevention Studies Branch (CPSB) and the Biometry Branch. The Cancer Prevention Studies Branch, located in the Prevention Program, contributes to the cancer control process by conducting controlled intervention studies. Intervention studies serve the dual purposes of confirming hypotheses

FIGURE 2

DIVISION OF CANCER PREVENTION AND CONTROL: PROGRAM RELATIONSHIPS



about cancer etiology and effecting cancer control, and act as a bridge between these two types of research efforts. The CPSB conducts intramural research in the areas of diet, nutrition and cancer, cancer chemoprevention, occupational cancer studies, and other cancer prevention strategies directed toward methods development and their application to reduce human cancer risk. The Biometry Branch, located in the Office of the Director, plans and conducts independent and collaborative studies in biostatistical and epidemiologic methodology and in mathematical modeling of processes relevant to cancer prevention and control activities. The Biometry Branch also provides consultation on statistical methodology and study design.

One of the factors behind the strong research program of the National Institutes of Health is the use of peer review in the development and evaluation of research programs. The need for peer review applies both to intramural as well as extramural programs. During the past eighteen months, both intramural branches have been reviewed by Committees of outstanding scientists representing the various disciplines relevant to the Branch research programs. Each Committee included members of the Division's Board of Scientific Counselors to assure that the intramural program is linked to the extramural program in the overall Division research strategies and that resources are allocated appropriately across the program areas.

The Committees addressed the depth and breadth of the Branch research programs, as well as specific needs and problems. The individual research projects were critiqued as to the quality of the research, progress, future directions, resources and staff development. Several recommendations were made and their impact will be reviewed in the future.

Division Director: Peter Greenwald, M.D., Dr.P.H.

Deputy Director: Joseph W. Cullen, Ph.D.

CANCER PREVENTION STUDIES BRANCH

OBJECTIVES

The major objective of the Cancer Prevention Studies Branch (CPSB) is to contribute to the cancer control process by conducting controlled intervention studies. Intervention studies serve the dual purposes of confirming hypotheses about cancer etiology and effecting cancer control, and act as a bridge between these two types of research efforts. Controlled prevention trials are most effectively conducted when appropriate intervention strategies are applied to high-risk populations. Etiologic studies serve to generate and support hypotheses that help identify such strategies and populations. In this context, preliminary supporting or exploratory studies that establish the feasibility of doing such interventions, and ancillary research efforts that assist in explaining intervention study results, are also necessary.

OVERVIEW

The CPSB conducts intramural research in the areas of diet, nutrition and cancer, cancer chemoprevention, occupational cancer studies, and other cancer prevention strategies aimed at lowering human cancer risk. This specifically involves:

- Planning, developing, and conducting nutritional and chemoprevention interventions and trials designed to test the effect of nutritional and chemopreventive agents in reducing cancer risk;
- Determining the safety, toxicity, pharmacokinetics, bioavailability, and mechanisms of action of various potential chemopreventive agents;
- Developing methods for assuring excellence in the performance of intervention studies; and
- Analysis of dietary, genetic, and lifestyle components of data obtained from existing national screening surveys and other data bases to assist us in (a) understanding cancer etiology, (b) selecting appropriate intervention strategies, including both high-risk populations and agents, and (c) understanding complex interactions of various dietary factors in relation to cancer incidence and mortality.

ACCOMPLISHMENTS

The Branch has initiated a number of intramural projects in 3 broad areas, including prevention trials, etiologic studies, and exploratory/explanatory studies. These projects represent collaborative efforts in investigating dietary, nutritional, and constitutional factors relating to cancer prevention. Following is a brief summary of the 8 currently active intramural projects, all but one of which will continue through and beyond FY 86.

Prevention Trials

U.S.-Finland Studies of Nutrition and Cancer (Z01 CN 00100 CPSB)

The important relationship of diet and nutrition in the development of cancer has become well known through various research efforts. Laboratory studies have shown cancer inhibitory function for various natural and synthetic nutrients in various models, which have been corroborated by human epidemiologic studies of nutrient intake, tissue levels, and cancer incidence. Vitamin A, beta-carotene, and selenium have been strongly implicated for their cancer preventive potential, with sufficient evidence for these substances to warrant their use in prevention trials. In addition, the roles of other nutrients in cancer cause and prevention (e.g., dietary fats and fiber) require further investigation.

The objectives of this cooperative project with the government of Finland are: (1) to determine if either beta-carotene or alpha-tocopherol supplementation is effective in preventing lung cancer in smokers; (2) to better assess the role of fats, selenium, and vitamins A,E, and C in breast cancer development; (3) to evaluate the relation of intake of various nutrients to subsequent cancer.

The project includes three studies. The first is a 5-year, randomized, double-blind, placebo-controlled, 2 x 2 factorial prevention trial of daily beta-carotene (20 mg daily) and alpha-tocopherol (50 mg daily) among smokers at high risk for lung cancer. The difference in lung cancer incidence between intervention groups will be determined. The second is a breast cancer case-control study of fats, total calories, selenium, and vitamins A, E, and C. The role of various anthropometric measurements as well as genetic markers for breast cancer will be explored. The third project will be a comparison of nutrient intakes in cases and references subjects identified from an existing large cohort with prediagnostic baseline dietary histories. Associations between various dietary components and several cancers will be assessed. Several pilot studies have been completed to date, and the prevention trial and breast cancer study are underway.

Use of Isotretinoin in Prevention of Basal Cell Carcinoma (Z01 CN 00103 CPSB)

This study is a 5-year, randomized, double-blind prevention trial designed to evaluate the effectiveness of low dosage levels of isotretinoin in reducing the incidence of basal cell carcinomas in a high-risk population, and to examine possible side effects associated with long-term administration of low doses of isotretinoin. Approximately 1200 evaluable subjects will be entered into the study within 18 months at 8 participating clinical centers located around the country. At each center, subjects will be randomly allocated to intervention (10 mg/day) or control (placebo) groups.

Vitamin A and its analogs, collectively known as retinoids, have been actively studied for several years in relation to their requirements in normal physiology and health, as well as for their potential in prevention of human disease. This vitamin is necessary for the differentiation of epithelial cells and is essential for the development and function of growth, reproduction, and vision. Deprivation or deficiency of vitamin A promotes tissue metaplasia and neoplasia in various animal and organ culture models. Supplementation with

retinoids can reverse these changes and restore functions of cell growth and differentiation in various cell lines.

Laboratory experiments have shown that retinoids administered to animals can prevent chemical carcinogenesis. Since in most of the experiments animals were administered retinoids after their exposure to the carcinogen, the prophylactic effect of the retinoids is believed to be in the post-initiation phase, i.e., during promotion of carcinogenesis. In addition, several epidemiologic studies have shown an association of low dietary intake or serum levels of vitamin A with increased risk of cancer, notably lung cancer and other tumors of epithelial origin. Recent case reports have shown that isotretinoin can prevent the appearance of new basal cell carcinomas for four years in patients at high risk of developing new tumors.

Nutrition Intervention Study of Esophagael Cancer in Linxian, China
(Z01 CN 00112 CPSB)

The purpose of this project is to conduct two intervention trials using multiple vitamin-mineral supplements to evaluate the relation between such supplements and esophageal cancer mortality. One trial is being conducted in patients diagnosed with esophageal dysplasia (n = 3,400) and the other in the general population (n = 30,000). Participants for the dysplasia trial were screened and recruited in the Summer of 1984 and distribution of active pills initiated in May, 1985. For the general population trial, screening/recruitment will be accomplished during the Summer, 1985 with active pill distribution anticipated for the Fall, 1985. The studies will evaluate the effect of these supplements on regression/progression of esophageal dysplasia, total cancer incidence, total cancer mortality, and total mortality. These two studies are being conducted in Linxian (Henan Province) in the Peoples' Republic of China (PRC). Linxian, a rural county with population of 800,000, was selected because it has the highest rate of esophageal cancer in the world, and because there is suspicion that the population's chronic deficiencies of multiple nutrients may be etiologically involved.

This study is being conducted jointly by the Biostatistics Branch of the Division of Cancer Etiology and the Cancer Prevention Studies Branch of the Division of Cancer Prevention and Control at the NCI in collaboration with the Cancer Institute of the Chinese Academy of Medical Sciences.

Lung Cancer Intervention Study Among Yunnan Tin Miners - Feasibility Study
(Z01-CN-00144-02 CPSB)

This pilot study will investigate the feasibility of conducting an intervention trial of micronutrients for the prevention of lung cancer among tin miners in Yunnan, China. The pilot will specifically be looking at general study logistics, ability to identify and recruit miners at high-risk, adherence to pill taking, potential adverse effects from intervention agents, quality control for data and sample collection/analysis, and baseline nutritional status among the miners.

Lung cancer rates are extraordinarily high among these miners. Males $\geq$ 40 years old with underground mining experience have a crude annual incidence of 1240×10^{-5} while miners aged 60-64 have an incidence rate in excess of 2500×10^{-5} annually. While the reasons for these high rates are not completely

known, the miners have been exposed to a number of known carcinogens, including tobacco smoke, radon and radon daughters, and arsenic. In addition, dietary intake of several micronutrients are thought to be inadequate.

This study is being conducted by the Cancer Prevention Studies Branch in collaboration with the Department of Epidemiology of the Cancer Institute of the Chinese Academy of Medical Sciences, and the Labor Protection Institute of the Yunnan Tin Corporation.

Etiologic Studies

The Analysis of Long-Term Followup (LTF) Data from the Breast Cancer Detection and Demonstration Project (BCDDP) (Z01-CN-00143-02 CPSB)

The BCDDP screening program began in 1973 in 29 centers in 27 widely dispersed geographic areas of the United States. Initial screening was completed on over 280,000 women over a 2-year period. From the original 280,000 participants in the screening phase of the BCDDP, approximately 64,000 were selected for 5 years of long-term followup (LTF) beginning in 1978, to assess the biology and natural history of breast disease, and to test hypotheses relating to detection, etiology, and survival. Those selected for LTF included all breast cancer cases found during the screening phase, all benign breast disease cases, all those recommended for biopsy, and a sample of "normals". The LTF data base will facilitate the exploration of important questions regarding the etiology and natural history of breast cancer. The size of the subcohorts and breadth of data available on them makes this population unique. The large number of cases of both breast cancer and benign breast disease with histologic information available should allow particularly useful analyses of several risk factors in relation these conditions.

The first 5 years of LTF will be completed in all centers by September, 1986 and further followup of the LTF subcohorts will begin then.

Linkage of Classical and DNA Markers to the Susceptibility Gene for Breast Cancer in High Risk Families (Z01-CN-00145-01 CPSB)

The overall goal of this project is to further an understanding of the genetic, environmental and cultural influences that are involved in the etiology of human breast cancer. The specific aim is to test for genetic linkage between a large array of discrete, polymorphic genetic markers and the gene(s) for breast cancer in family data. The ultimate goal is to localize a gene or genes that predispose women in high risk families to breast cancer. A sample of women with a strong family history of breast cancer who participated in the Breast Cancer Detection Demonstration Project (BCDDP) will be contacted and pedigree, vital status, health history and epidemiological data will be collected from them and their family members. Fifteen to twenty families whose pedigree structure appears to be the most informative for use in linkage analysis studies will be selected. Blood will be collected from family members and analyzed for the presence of a number of genetic markers, including blood group antigens, red blood cell enzymes, plasma proteins and restriction fragment length polymorphisms (RFLPs). Marker data results will then be used to perform computer generated linkage analysis.

This project is expected to start September, 1986 and continue for 3 years.

NHANES I Epidemiologic Followup Survey: Chemoprevention/Nutrition Aspects (Z01 CN 00104 CPSB)

The purpose of the NHANES (National Health and Nutrition Examination Survey) Initial Epidemiologic Followup Survey was to conduct a longitudinal study of 14,407 adults originally surveyed in 1971-75, to investigate subsequent health and mortality outcome. Respondents were traced and re-examined. Information was obtained from hospital records, the National Death Index, and death certificates. The NHANES Initial Followup Survey was completed in 1984. The purpose of this intramural project is to examine the relation of chemopreventive, nutritional, and constitutional factors to cancer in the very large, representative population which NHANES offers. It provides an opportunity to examine these factors and potentially confounding or modifying factors in a prospective fashion, and to examine the effectiveness of dietary agents which are currently of great interest for cancer prevention. The relation of baseline vitamin use, biochemical or nutritional measures, and subsequent health status will be examined. A Continued Followup of the elderly (> 75 years old) in this cohort started in 1985, while the entire cohort will be followed up in 1986.

Exploratory/Explanatory Studies

Human Studies of Diet and Nutrition (Z01 CN 00101 CPSB)

The role of dietary factors in cancer prevention has been assessed in animal experiments, in human epidemiologic studies, and, most recently, in prevention trials. For many of these agents, however, information is incomplete concerning their safety, toxicity, dose, form, bioavailability, pharmacokinetics, and mechanism of action. To further define these parameters in humans, a cooperative research effort between the Beltsville Human Nutrition Research Center (BHNRC), U.S. Department of Agriculture, and the CPSB, DCPC, is being conducted. The overall goal of this collaborative effort is to obtain further information on potential cancer preventive agents. Initial efforts have focused on 3 nutrients which have shown the most promise for cancer prevention -- selenium, fat, and beta-carotene.

A study of the kinetics of a single, oral dose of two forms of selenium in the fasting and non-fasting state was conducted in the first year. Current activities include evaluations of the safety/toxicity of selenium and form of ingestion among persons residing in seleniferous areas.

Our first study of fat focused on potential mechanisms of action and will assist us in the evaluation of the relation of type and amount of dietary fat to hormonal status, bile acid metabolism, and fecal mutagenic activity in premenopausal women. Subsequent evaluations will examine the relation of dietary fat and fiber to bile acid metabolism and fecal mutagens in men.

Beta-carotene studies are examining the plasma carotenoid response to single and long-term ingestion of beta-carotene from either a capsule or from selected vegetables.

PLANS

For the immediate future we expect to continue to consolidate the numerous activities that have been initiated by the Branch since its inception just 3 years ago.

We expect prevention trials to continue to be our major activity and we will continue to look for unique opportunities for trials, both within the U.S. and in foreign countries. Our focus will continue to be those cancer sites whose prevention will contribute the most to a reduction in cancer morbidity and mortality.

In the area of etiologic studies we will continue to work with existing data bases available to us.

Explanatory/exploratory studies conducted collaboratively with the Beltsville Human Nutrition Research Center will continue for the immediate future to focus on the safety and form of selenium we ingest, the effect of varying types and levels of fat and fiber on bile acids and fecal mutagens, on the pharmacokinetics of carotenoids, and on in vivo measures of lipid peroxidation.

STAFF

Acting Branch Chief:	Peter Greenwald, MD, DrPH
Acting Deputy Branch Chief:	Philip R. Taylor, MD, SM
Pharmaceutical Research Coordinator:	Joseph A. Tangrea, RPh, MPH
Staff Fellows:	Demetrius Albanes, MD Christine Carter, PhD, MPH D. Yvonne Jones, PhD Marc S. Micozzi, MD, MSc Arthur Schatzkin, MD, DrPH Christine Swanson, PhD, MPH
Research Associate:	Jan Morgan, RPh
Research Study Coordinator:	William Campbell, RN
Visiting Fellow	Qiao You-Lin, MD, MPH
Secretarial Support:	Markita Garner Nina Steele

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OBJECTIVES

The overall objectives of the Biometry Branch are summarized in the functional statement:

- "Plans and conducts independent and cooperative research studies concerning cancer epidemiology, prevention, screening, diagnosis, treatment, and control using methods of mathematical and analytic statistics;
- plans and conducts independent and collaborative studies in biostatistical and epidemiologic methodology and in mathematical modeling of processes relevant to cancer prevention and control activities;
- provides consultation and review of proposed projects concerning biostatistical methodology and study design to staff of the Division and to investigators in other divisions of the NCI and outside;
- provides expertise in statistics and biometry to management and scientific decision-making meetings within the NCI and outside."

OVERVIEW

The work of the Branch is conducted via three Sections and by the Office of the Chief. The principal projects underway in each of these four organizational units will be described separately. The functional statements for each of the three sections will precede the description of their projects. Projects that involve collaboration across Sections or with the Office of the Chief have been placed arbitrarily in this report to avoid duplication.

OFFICE OF THE CHIEF

Year 2000 Projections

A comprehensive interactive Fortran program has been written to project cancer mortality and incidence figures (numbers and rates) from 1980 through 2020 (Z01-CN-00142-02 SORB). The program incorporates two difference survival models (Weibull and mixed exponential), 40 cancer sites, the ability to begin with or without prevalent cases, temporal trends in underlying cancer incidence and in mortality from other causes, three possible interventions (primary prevention, screening, and treatment), age adjustment, calculation of annual incidence and mortality statistics, and comparison of these statistics under changing conditions of trends and interventions. The Biometry Branch staff work closely with SORB staff. Work during the past year has included continued modification of the computer model and generation of detailed projections used by the DCPC in its monograph on "Cancer Control Objectives for the Nation."

Community Intervention with Heavy Smokers

Extensive consultation has been provided to the staff of the Smoking, Tobacco, and Cancer Program concerning design issues which have arisen in the planning stages of a large-scale community-based study intended to promote smoking cessation among heavy smokers. Staff of the Biometry Branch have devised the basic design for the study, eight matched pairs of communities with one member of each pair to be chosen at random for intervention and the other serving as a control. Based on smoking cessation data from the MRFIT study we believe that this design will allow about 90% power for detecting a 10% difference in the smoking quit rate between the intervention and control communities, but even if our assumptions are wrong concerning the applicability of the MRFIT data for estimating variances, a non-parametric analysis using the sign test will still be significant if seven out of eight or all eight pairs show greater quit rates among heavy smokers in the intervention communities. During the past year the RFA's for the coordinating center and the intervention sites have been released and proposals have been evaluated for selecting the participants. The protocol will be worked out specifying the nature of the interventions to be studied in a series of six three day meetings in the coming year.

The Women's Health Trial

The Women's Health Trial is a large-scale randomized cancer prevention study designed to test whether or not a low fat diet will reduce the incidence of breast cancer in high risk women. In November of 1985 the Biometry Branch held a one day workshop to review and discuss the statistical issues in the design of this trial because since the inception of the idea the estimates of sample size needed for adequate power to test hypothesis had risen from 6000 to 30,000 subjects. The reasons for this change were reviewed and it was concluded that the larger number, based on using two-sided significance tests and on more realistic estimates of breast cancer incidence among high risk women, was appropriate. Since that time the Branch Chief has taken on major responsibility as a scientific advisor to this trial and helped set up a second workshop in June of 1986 to review the best available data and hear opinions of experts concerning whether or not the diet used in the full scale trial should be designed to lower serum cholesterol as well as fat intake. It was decided that such a diet would be tried out for about a year to verify feasibility and acceptability. In addition the workshop revealed such a paucity of data pertinent to the decisions that need to be made that it was also decided that two metabolic feeding studies should be carried out, one testing the diet the women in the feasibility study reported that they were eating, and the new diet designed to lower cholesterol. The Biometry Branch will be heavily involved in the design, conduct and analysis of these studies in collaboration with members of the Cancer Prevention Studies Branch.

Morbidity Among Long-Term Survivors of Childhood Cancer and Their Offspring (Z01 CN 00114-03 BB)

This study, done in collaboration with investigators in the Division of Cancer Etiology, was designed to detect the effects of cancer and its treatment on childhood patients who survived to adulthood, as well as any effects that might have been transmitted to their offspring. The study, a retrospective-cohort-with-sibling-control design, investigated the occurrence of subsequent primary cancers, quality of life, late morbidity other than cancer, infertility among the cases, and cancer and birth defects among offspring.

Cases selected from five U.S. cancer registries were patients under 20 years of age with a histologically confirmed malignant neoplasm or brain tumor diagnosis, and who reached the age of 21 years. Up to two sibling controls were selected for each case with sequential priority given to full blood relationship, same sex, closest in age. Interviewer-administered questionnaires were obtained for 2,285 (91 percent) cases and 3,265 (91 percent) controls.

Cancer occurred in 7 of 2,308 offspring of surviving cancer patients and in 11 of 4,719 offspring of their sibling controls, a non-significant difference. Two of the seven cancers among offspring of surviving cancer patients were accounted for by hereditary retinoblastoma; one by hereditary Wilms' tumor and one by Sipple's syndrome.

Of all survivors of childhood and adolescent cancer, only those with central nervous system (CNS) tumors experienced a deficit in educational achievement as measured by completion of eighth grade or high school. The major effect for CNS patients was noted for completion of eighth grade: 88 percent for survivors versus 100 percent for their siblings (RR=0.88, 95% CL 0.85-0.92). Among those CNS patients who completed the eighth grade there was no further reduced rate of completion of high school.

The relative risk among married subjects (surviving cancer patients versus their sibling controls) of establishing at least one pregnancy was 0.73 (95% CL 0.69-0.79). The reduction in risk of establishing a pregnancy was in part a function of treatment of the index cancer. For surviving male patients the major risk reduction was associated with alkylating agent chemotherapy (RR=0.33, 95% CL 0.21-0.51) while for females the largest effect was due to radiation therapy (RR=0.56, 95% CL 0.43-0.73). Relative risks for combined effects of radiation plus alkylating agent chemotherapy were 0.28 for male and 0.52 for female cancer patient survivors. Thus, the combination of radiation and alkylating agents did not appreciably alter the risk when compared to the major single modality effect for each sex.

BIOSTATISTICAL METHODOLOGY AND CANCER CONTROL EPIDEMIOLOGY SECTION

The overall objectives of the Section are summarized in its functional statement:

- "Plans and conducts independent and collaborative research concerning biostatistical and epidemiologic methodology related to cancer prevention and control;
- conducts or collaborates in the design and implementation of studies aimed at developing, refining, and testing hypotheses relating to applied cancer prevention and control, community oncology, and diffusion and adaptation of effective prevention, control, and treatment technologies;
- plans and conducts independent and cooperative studies into the theory and analysis of cancer prevention and control;
- provides statistical consultation both within and outside the NCI to researchers concerned with problems related to Section responsibilities and staff expertise."

Models to Estimate Effect of Smoking on Lung Cancer

Lung cancer has long been linked to the smoking of cigarettes. Epidemiologic and experimental evidence points to smoking having a carcinogenic effect at both an early stage and a late stage in the cancer process. The purpose of this project is to quantify the magnitudes of these two effects in order to derive optimal intervention strategies. The results of a large European multicenter case-control study of lung cancer were used to estimate the relative effects of cigarette smoking upon the initial and penultimate events in a presumed multistage cancer process. These estimates indicate that the predominant effect of cigarette smoking is upon a late stage in the development of lung cancer.

Models to Estimate the Effect of First Pregnancy on Breast Cancer

Epidemiologic and experimental evidence points to hormones as playing an important role in the development of breast cancer. Women with an early menarche and a late menopause have been found to exhibit a high risk of breast cancer. Pregnancy has also been found to be an important modifying factor in both human breast cancer and that induced in experimental animals. Women who have had their first full-term pregnancy at a young age are at lower risk than women who had their first child at a later age. The risk for nulliparous women falls in between these two extremes. Experimental studies have indicated that the first full-term pregnancy produces two competing effects on the development of mammary cancer in rats, one protective and one which increases risk. The purpose of this project is to apply a two stage carcinogenesis model Moolgavkar and Knudson (JNCI 66, 1981) to the results of the BCDDP case-control study of breast cancer in order to estimate the magnitude of these competing effects. Conditional regression techniques are planned to be used.

Lung Cancer Mortality Trends

The purpose of this work is to project the future course of age-specific lung cancer mortality in the U.S. which would be expected if current trends persist without any specific population intervention. The statistical method being used is an age-period-cohort model which relates the mortality rate to an individual's age, his year of birth, and the calendar year of observation. The data used for these analyses are the sex- and age-specific lung cancer mortality rates for the period 1958-1982. The period and cohort components of the observed mortality trends will be projected into the future for each sex separately based on projected smoking behavior patterns and changes in average cigarette tar content. The results of the 1978-1980 Health Interview Survey smoking supplement will be used to correlate past smoking behavior with current cancer mortality in order to relate these mortality projections to predictions of future patterns in cigarette smoking.

Interactive Time Trend Analysis Program

The purpose of this project is to develop a set of interactive computer programs permitting easy analysis of trends in cancer rates over time. One program will allow the user to define a particular Poisson regression model which includes effects for age, year of birth, for calendar year of observation, sex, and race. A second program will allow the user to construct plots of age-specific mortality rates by calendar year or by year of birth, as well as plots of the various parameters in the regression models. The data used by these programs are U.S. sex-, race-, age-, and site-specific mortality rates for the period 1958-1982 (data for later years will be added when available), and international data collected by the World Health Organization which we obtained through the National Center for Health Statistics.

Solution to the Non-Identifiability Problem in Age-Period-Cohort Models

Age-period-cohort models applied to a table of counts of cancer cases by age and calendar period are being used with increasing frequency for the analysis of cancer incidence/mortality trends. However, these models suffer from one major weakness - the linear components of the three factors cannot be uniquely estimated without putting some constraint on the parameters and the resulting estimates have been shown to be sensitive to the particular constraint employed. Thus estimation of the separate period and cohort components of time trends are suspect. This research has found that this non-identifiability problem can be solved by adding a birth cohort dimension to the table of observed counts of cancer cases. The solution uses demographic methods to disassemble counts aggregated by 5-year age groups into counts by single years of age which are then divided into counts by age and year of birth and finally reassembled into 5-year groups by age, calendar period, and year of birth cohort.

Mathematical Models of Drug Resistance to Anti-Tumor Agents

The Coldman-Goldie (Math. Bioscience, 1983) model for resistance to anti-tumor drugs is extended to very general situations involving different patterns of drug effects and nonhomogeneous stochastic birth and death of tumor cells. The probability distributions and cumulants of the numbers of tumor cells sensitive and resistant to drug treatment under various conditions have been developed. This research makes it possible to predict the success of chemotherapy under complex situations involving different patterns of drug applications, drug resistance, and the cell killing effect of treatment.

Multiple Pathway Model of Carcinogenesis

Many human cancers appear to be developed from normal cells by more than one pathway (Holman, Armstrong and Keenan JNCI, 1983; Albert International Conference on Mechanism of DNA Damage and Repair, June 2-17, 1985, National Bureau of Standards, Gaithersburg, Maryland). For studying cancer prevention and control, this research develops the mathematical theory for multiple pathway carcinogenesis models and obtains expected incidence curves for the tumors produced through the different pathways.

Descriptive Cancer Epidemiology (Z01 CN 00115-03 BB)

Trends in Mesothelioma Incidence in the U.S.

Trends in mesothelioma incidence rates based on data from the SEER Program during 1975-84 were studied. There were 609 cases diagnosed during 1975-79 (an average of 122 per year) compared to 860 (172 per year) during 1980-84. The average annual age-adjusted incidence rate among white males increased from 5.9 to 7.6 per million population during these time periods. Pleural mesothelioma among males accounted for 405 cases in 1975-79 (8.9 cases per million) and 583 cases in 1980-84 (12.0 cases per million). Analyses using Poisson regression models for the effects of age, period, and cohort showed that white males in the 1905-09 birth cohort experienced higher rates for pleural mesothelioma than those in earlier or later birth cohorts. This is thought to be related to work-place exposure to asbestos during World War II.

Prognostic Significance of Serial Epstein-Barr Virus Antibody Titers in Treated Nasopharyngeal Cancer Patients

Antibody titers to Epstein-Barr virus (EBV) antigens among nasopharyngeal carcinoma (NPC) patients fluctuate during the course of disease. An assay pattern that is predictive of treatment effectiveness would be very useful for monitoring patients' prognosis. The proportional hazards model with titer measurements treated as a time-dependent covariate is being used to evaluate the prognostic significance of antibody titers to EBV nuclear antigen (EBNA) and EBV early antigen (EA). Forty-eight Chinese NPC patients whose sera were analyzed for these EBV titers and treated at the same hospital in Hong Kong provided 288 serial serum samples. The samples were taken at the time of diagnosis and at 4 to 6 month intervals over the first 5 years of follow-up. The prognostic significance of each antibody titer evaluated separately has indicated an increased risk of death being significantly associated with the level of the most recent titer prior to death. An evaluation of the prognostic significance of titer time patterns (e.g., lagged titer measurements, change in latest two measurements), as well as joint analysis of the two titers is being conducted.

Cancer in Oriental Populations (Z01 CN 00113-03 BB)

Cancer in Oriental Populations

U.S. Asians are among the most rapidly growing ethnic segments of the population. With the advantages of being concentrated in a few large areas, having relatively distinctive lifestyles, and having homeland data available for comparison (at least for the three largest groups of Chinese, Filipinos, and Japanese), studies of these groups to determine the effects of migration on cancer risks continue with the aim of developing appropriate preventive and control programs.

Cancer Patterns for Orientals in the U.S.

The study of health risks of Chinatowners as compared to the general Chinese population was completed. Despite the differences in socioeconomic characteristics between the two areas, no consistent statistically significant differences in health risks were observed. The site-specific cause of death risk levels appeared to be internally consistent as well as compatible with relevant study results for U.S. Japanese migrants.

Cancer risks for Chinese, Japanese, and Filipinos in SEER areas (incidence, mortality, and survival) and in the U.S. as a whole (mortality) continue to be updated and analyzed, pointing to possibilities for specific preventive programs. Area differences between Hawaii and San Francisco, many long standing, have been observed, e.g., higher rates of lung and liver cancers in Hawaii for all three ethnic groups. Regardless of site-specific variations in risk level between whites and each U.S. Asian group, the rank order of leading sites are similar, i.e. lung, colon, and prostate for males and breast, lung, and colon for females.

Inter-country Cancer Pattern for Chinese and Other Asian Groups

Following the completion of the study of cancer mortality among Chinese in the U.S., Hong Kong, and the People's Republic of China (PRC), a second study comparing migration effects of Chinese in Taiwan and Singapore with their predominant homeland area of Fujian Province in the PRC was undertaken and is nearing completion. Risks for stomach and esophageal cancers are much lower in both Taiwan and Singapore compared to Fujian, but only small differences were observed for colon, rectum, uterus, and leukemia. Findings of this and the earlier study are being analyzed together for site-specific similarites and differences between U.S. and Asian migrants.

For the Chinese in China, an analysis based on a review of pertinent literature is being made of the health status of this population for the years before and after the establishment of the PRC in 1949. The more detailed examination of cancer mortality, mainly drawn from the 1975 National Mortality Survey, has its emphasis on etiologic interventive clues and cancer mortality transition.

Incidence and mortality data for both U.S. Japanese and Filipinos are being compared with those for Japan and the Philippines.

U.S. Japanese are potentially valuable to study since they are long time residents and have had only a small influx of new immigrants. Levels of cancer risk for some sites remain similar for both countries, such as low risks for buccal cavity, lung and bladder, but other risk levels have changed greatly, some reaching similar levels to those of whites, e.g., esophagus, colon, and cervix.

U.S. Filipinos more than doubled in numbers between 1970 and 1980, and now rank with Chinese and Japanese in size. Compared to data available for the Philippines, rates for U.S. Filipinos have increased sharply for such sites as colon, rectum, lung, prostate, and breast, but declined for cancers of the stomach and liver.

Future Plans

On the cross-continental level, a case-control study is being planned to examine lung cancer among never-smoked Chinese females in Guangzhou (China), Hong Kong, Singapore, U.S. Bay Area, and New York City. Not only is it time that the majority of Chinese females at home and abroad do not smoke, cancers arising in those who never smoke also contain a high proportion of adenocarcinomas, a cell type thought to be least likely related to smoking. Also, among Chinese females with lung cancer, those who had never smoked were significantly younger than those who had ever smoked.

For Chinese in China, data are being obtained to compare the findings of mortality of cancer and related diseases in a 65 county sub-sample with those based on the parental 1975 National Survey to ascertain internal consistency.

For Chinese and Japanese, data are being obtained for the years around 1980 by nativity for the U.S. and for homeland areas, to extend the 1960 and 1970 mortality studies to a two decade trend analysis. New insights are anticipated particularly from analysis of age specific rates because of the inclusion of a sizeable number of American born population at the older cancer ages.

Development of Cancer Control Epidemiologic Methods (Z01 CN 00122-02 BB)

The purpose of this project is to develop the methodology of cancer control epidemiology, with emphasis on its conceptual foundations in biological, statistical, and epidemiological theory. Research areas include: concepts of cause and prevention; the logic of epidemiologic inference, the structure of causal and preventive models, the relationship of biological models of carcinogenesis to causal and preventive models and to models of interactions, problems of self selection and selection bias, the role of case-control methodology in studies of early detection, and the scientific, technological and ethical implications of cancer control epidemiology. Some specific examples of work underway in this project include:

Studies in Causal and Preventive Inference

Strong inferences are important to any scientific study, but they are especially important in cancer control epidemiology, because results may be translated directly into practice as preventive measures. In this project, an examination of methods of inference in cancer control epidemiology continues. Two specific areas of inquiry are the use of inductive and deductive logic in epidemiologic explanations, and the problem of causal criteria.

In the first of these areas, the origin, consistency, testability, and permanence of epidemiologic explanations have been examined in terms of inductive and deductive logic. Deduction proves superior as long as it is tied to the concept of refutability. In practical terms this means that hypotheses which yield precise deductions are to be preferred because they are more easily refuted. It follows that among competitors, the better hypotheses are the ones which best survive attempts at refutation.

In the second area of inquiry involving epidemiologic inference, the traditional causal criteria have been examined in terms of a critical deductive method. Hypothesis-dependent criteria include strength of association, biologic gradient, temporality, preventability, consistency, and specificity. Other criteria such as plausibility and coherency were shown to be related to predictability and testability. Although the causal criteria have been used to help epidemiologists decide how to act on the basis of research results, our inquiry reveals that it is more important to consider three basic decision techniques: belief, probability, and criticism. Of these, criticism is the most important.

Criticism is also an important component of problem-solving methods. A topic of current research is the development of a general problem-solving method for cancer control epidemiology. It will be applied to the evaluation of progress in methodologic research.

One of the causal criteria, namely strength of association, has also been singled out as a topic for future research. Specifically, the plan is to criticize the long-held notion that the greater the magnitude of an observed association, the more likely the association is causal.

Studies in Causal and Preventive Interactions

The role of interaction in epidemiologic research is controversial. At least three categories of interaction have been identified: biological, statistical, and public health. A general examination of the links between these categories of interaction was undertaken in order to define these ideas more precisely. It was concluded that although simple statistical models of interaction are testable, limiting attention to additive and multiplicative models alone may be inadequate unless they can be tied to more explanatory biological theories.

It has also been found that, contrary to current thinking, the additive model of causal interaction and the multiplicative model for preventive interaction should not be used as thresholds for recommending public health actions. Instead, these decisions should be based upon the balance between the risks and benefits of removing one interacting factor or the other. Such decisions are generally independent of considerations regarding whether some threshold level for combined risk has been exceeded.

Selection Bias and Generalizability

Selection bias may interfere with the generalizability of results from intervention studies, because the results from studies on highly selected groups may be the only data available for predicting the effects of applying interventions to large populations. One example of this kind of selection is the healthy worker effect. In a recently completed study, in which the mortality experience of a large nationally distributed population of communications workers was compared to the general U.S. male mortality, a theory for the healthy worker effect was successfully tested. A modification of this theory is underway, with plans to test it both in the original data and in a larger population comprised of U.S. veterans.

Future Research

Planned research activities include: the development of the conceptual foundations of cancer control epidemiology with special emphasis on the first two phases of cancer control research: hypothesis development and methods of development.

CLINICAL AND DIAGNOSTIC TRIALS SECTION

The overall objectives of the Section are summarized in its functional statement:

- "Engages in independent and cooperative research on statistical methodology for design of controlled clinical trials of cancer prevention and treatment and for field testing of diagnostic techniques;

- provides full statistical support in selected trials, including development of the detailed study plan, supervision of data collection, processing, and editing, and analysis of the data as well as preparation of scientific papers;

- develops statistical techniques for analyzing trial results, for identifying prognostic factors and diagnostic determinants, and for analyzing observational data;

- consults and collaborates extensively with other researchers requiring expertise in these and related areas."

Statistical Methodology Research (Z01 CN 00116-03 BB)

Methodology of Sample Size Determination for Prevention Trials

Existing methods of sample size estimation were adapted for planning cancer prevention trials. Subjects entering these trials may have pre-existing cancers and thus not be susceptible to the intervention. Including such cases as trial outcomes will underestimate the true intervention effect. Pre-screening before trial entry may remove some of these cases. Since no screen is perfect, their effect can be mitigated, but not eliminated. It appears that in the context of prevention trials, sample size will always have to be increased; the greater the dilution effect, the greater the increase in sample size needed at the planning stage.

Methods of calculating sample size to compensate for the dilution effect have been developed for trials where the proportions test is appropriate. Expected event rates are dependent on estimates of disease prevalence, incidence in the screened population, screening test sensitivity and specificity. A simple cost model has been developed which allows overall assessment of the costs of screening compared to the costs of the larger sample that would be required without screening.

Simulation Methods for Sample Size in Trials with Arbitrary Hazards

The usual methods for sample size determination in randomized clinical trials rely on simple parametric assumptions regarding accrual, survival, and censoring and are not applicable to the general case of different hazards in each treatment group. This work involves computer simulation methods in which the user specifies arbitrary hazards for survival and censoring in the treatment groups, and the power of the trial is determined by simulation. Sample sizes can be adjusted until adequate power is achieved. Power calculations have been performed for certain types of hazards such as delayed treatment effectiveness.

Sample Size Computer Program

Development has continued on a program to compute power and sample size for a variety of experimental design situations. The program operates interactively on the NIH DEC-10 computer system. The user may specify the total time patients are accrued in a trial, length of follow-up after patient accrual is completed, drop-in or drop-out of patients from assigned treatment groups, stratified designs, and patient loss to follow-up. Calculations are also available for matched and unmatched case-control studies, comparison of means, and designs where several groups are compared using the F-test.

The program is user-friendly and prompts for answers to design questions. Optional user instructions provide a description of program capabilities as well as citing literature from which equations used in the calculations were adapted. Future capabilities will include exact power calculations for comparing two means with a t-test, and "proving" the null hypothesis (e.g., testing the equivalence of two modalities).

Development of Sample Size Methodology for Matched Studies

In a matched study (e.g., case-control) each control does not have the same probability of exposure or disease outcome. Hence there is a distribution of probabilities over all the controls. Sample size requirements for the three models of constant odds ratio, relative risk, and difference of probabilities gave markedly different sample sizes than those for the comparable unmatched situations. In particular the constant odds ratio increased the sample size while the constant risk and the constant difference decreased the requirement. This indicates that applying sample size formulae for unmatched situations in an attempt to be conservative will grossly underestimate sample size for the constant relative odds.

Regression with Errors in Variables

It is well known that regression analyses can be heavily biased if independent variables (covariates) are measured with error. In particular, studies relating cancer to diet and lifestyle are prone to such biases, so it is important to devise statistical methods to compensate for errors in variables.

Methods for correcting logistic regression for errors in variables have been developed when replicated covariate measurements are unavailable, based on maximizing an approximate likelihood. In large samples, this technique reduces the bias by an order of magnitude. The required computations have been programmed in FORTRAN, making the new methods available to practitioners. Simulation studies will demonstrate the accuracy of the asymptotic theory in finite samples, and will investigate questions of robustness and small sample efficiency.

Analysis of Cancer Maps

Spatial data are widely used for hypothesis generation, but present special methodologic problems. Work has continued on using linear regression methods to model such data, while accounting for the dependence among neighboring geographic regions. These methods have been applied to breast cancer and oral cancer in an effort to generate etiologic hypotheses.

Qualitative Interactions

Instances where treatment effects are positive in some subsets of patients and negative in others are uncommon, but are of particular interest to investigators. This work has focused on the power of two recently proposed tests for such situations. Results indicate for which type of alternatives one or the other test might be more powerful.

Cost of Clinical Trials

This work focuses on accrual and survival as the major determinants of the variable costs associated with clinical trials. A simple cost model was based on accrual and survival models and was studied for treatment and prevention type trials. The behavior of cost as a function of time was shown to depend heavily on the ratio of patient accrual cost to follow-up cost.

Interactive Data Analysis Programs

The Section has previously developed and continues to maintain and improve a group of interactive computer programs for efficient analysis of medical data, particularly that dealing with risk factors and prognostic factors using sophisticated multiple regression techniques and survival analysis. These programs have proven useful not only for many projects within the Biometry Branch but also elsewhere in the Division, as well as by other investigators both within the NIH and at outside institutions.

Consultation on Clinical Trials and Other Studies (Z01 CN 00119-03 BB)

Lung Cancer Clinical Trials

The Section provides full statistical support for the Lung Cancer Study Group. This group of nine major medical centers was formerly supported by contract with the Division of Cancer Treatment (DCT), but has been successful in competing for continued support under a cooperative agreement. The primary emphasis of these protocols is the study of adjuvant chemotherapy, radiotherapy, or immunotherapy in patients with resected lung cancer. Currently, some 350 patients annually are accruing to nine protocols, four protocols are in the follow-up phase, and replacement protocols are being developed. Results from several of these protocols provide evidence that combined chemotherapy (cytoxan, adriamycin, cis-platinum) may prolong survival in patients with non-small cell lung cancer. Radiotherapy is under investigation in several protocols. Also, protocols have been developed to evaluate the role of surgery following a course of chemotherapy and/or radiotherapy designed to render inoperable patients operable. The role of surgical resection following induction chemotherapy in small cell lung cancer is being investigated in collaboration with the EORTC. A new study has been initiated to test the role of early versus late chemotherapy in surgically resected lung cancer patients. Special studies regarding the prognostic effect of blood transfusion, brain recurrence, patterns of nodal involvement, and the importance of cell type in recurrence have been undertaken.

Brain Tumor Clinical Trials

The Section provides full support for the Brain Tumor Cooperative Group, a multicenter group of neurosurgeons, neuro-oncologists, radiotherapists, neuroradiologists and neuropathologists conducting randomized trials for patients with primary brain tumors (with emphasis on malignant gliomas). There are currently two randomized trials accruing patients: BTCG 83-01 is a phase III study with a factorial design comparing intra-arterial versus intravenous BCNU, with and without intravenous 5-FU, for the post-operative treatment of malignant glioma (concurrent with radiotherapy). BTCG 84-20 is a phase II comparison of intra-arterial cisplatin versus intravenous BCNU for primary brain tumors. In

addition, the Group is currently evaluating interferon in a non-randomized phase II study. During the past year, data were analyzed and presented for a previous phase III study, BTCG 80-01, comparing 3 different chemotherapy approaches and also comparing 6000 rad whole brain irradiation versus 4300 rad whole brain plus 1700 coned down to the tumor volume. The conclusions were that giving part of the radiotherapy by coned-down port was as effective as full whole brain irradiation, but that giving multiple drug chemotherapy as outlined in the protocol conferred no significant survival advantage over BCNU alone. Additional subsidiary analyses are underway using BTCG data to study prognostic factors related to pathology and CT scan results, and to study presenting signs and symptoms of these patients.

Multiple Regression Analyses of Risk Factors for Breast Cancer

In collaboration with the Cancer Prevention Studies Branch, data from the National Health and Nutrition Examination Survey (NHANES) are being analyzed to investigate dietary risk factors for breast cancer while adjusting for other known risk factors. In collaboration with the Epidemiology and Biostatistics Program, DCE, data from the Breast Cancer Detection Demonstration Project (BCDDP) and from the Cancer and Steroid Hormone Study (CASH) are being analyzed to investigate risk factors which could be used to advise women on their breast cancer risk. The analysis of BCDDP data extends a previous analysis on the risk attributable to multiple factors; these results are applicable to the planning of prevention trials. Finally, in collaboration with the Cancer Prevention Studies Branch, other data from the BCDDP, which include additional prospective follow-up, are being analyzed looking at various aspects of benign breast disease as risk factors for subsequent development of cancer.

Serum Markers for Breast Cancer

Serum and background information have been collected from over 12,000 women for evaluation of biological markers for breast cancer. Shipments of blinded panels of serum were sent on request to qualified researchers during the past year. Investigators used monoclonal antibodies in attempting to discriminate among sera from control, benign and breast cancer groups. Others studied Interleukin-2 receptors or used RIA to detect DF3 antigen levels. Another researcher studied the neutralization of virus-mediated cytotoxicity and demonstrated higher assay values in early stage breast cancers. This promising result prompted a second shipment to this researcher. When the results of the assays of blinded sera are completed, the data are returned to the Clinical and Diagnostic Trials Section for analysis, and these analyses and unblinded data are returned to the investigators.

Selenium Pharmacokinetics Study (Z01 CN 00107-04 BB)

Selenium is a possible cancer preventive agent, and is being considered for use in intervention trials. A study in collaboration with the Cancer Prevention Studies Branch (Z01 CN 00101-04 CPSB) is in progress which will provide information on the pharmacokinetics of selenium in its prototype forms—sodium selenite (inorganic form) and selenomethionine (organic form). This information is necessary for the determination of time and manner of administration. A kinetic model for selenite has been developed. Parameters such as percent absorption, maximum concentration, time to maximum concentration, and mean residence times

will be estimated for a single dose and compared in fasting and non-fasting subjects.

Population Consumption of "Protective" or "Harmful" Foods

In order to carry out prevention programs aimed at reducing cancer incidence through dietary modifications, it is necessary for policy-makers to have a clear picture of the current American diet. A study examining the consumption of specific foods and food groups in the American diet, focusing on those foods thought to be harmful or protective with respect to the development of cancer, is underway in collaboration with the Surveillance and Operations Research Branch (Z01 CN 00111-03 SORB) and the National Center for Health Statistics. The study uses twenty-four hour dietary recall data collected in the second National Health and Nutrition Examination Study (NHANES II). Individual NHANES II food codes were combined into food groups; the choice of groups was based on the literature on diet and cancer and the interim dietary guidelines of the National Research Council report in Diet, Nutrition and Cancer. Foods under study which are thought to be protective include fruits, vegetables (all, garden, cruciferous, deep yellow and leafy green), fruits and vegetables high in vitamin A or high in vitamin C, and breads and cereals high in fiber. Foods considered potentially harmful include red meat and meats containing nitrites (bacon, hot dogs, luncheon meats). Consumption of poultry and fish is also being investigated. The analysis is being stratified by sex, race, age group, poverty index, and region (Northeast, South, Midwest, and West). As NHANES II data comprise a representative national sample, national estimates can be made of the proportions of Americans consuming foods in the above groups. For example, estimates show that less than 60 percent of the population ate any vegetable (excluding potatoes and salad); the proportion eating any cruciferous vegetables was only 13 percent. In addition, because of interest in the role of dietary calcium in the prevention of colon cancer, a study of the consumption of low fat and whole milk, similar in format to the study above, is currently underway.

Study of Food Purchasing Behavior and Consumer Nutrition Education

The Clinical and Diagnostic Trials Section is providing statistical support to a nutrition project being planned jointly by the Surveillance and Operation Research Branch of the NCI and Giant Food, with the goal of cancer risk reduction. Consultation is being provided on study design and plans for data analysis.

The National Death Index

The National Death Index (NDI) offers an efficient method of ascertaining mortality and subsequently obtaining cause of death for the large numbers of persons involved in studies conducted or funded by the NCI. Efforts to acquaint cancer researchers with the NDI and its uses in treatment and prevention trials and in epidemiologic and occupational studies began in 1984, continued in 1985, and included a poster presentation at the meeting of the Society for Clinical Trials in 1986. A paper, written in collaboration with the National Center for Health Statistics (NCHS), suggesting potential uses of the NDI as a tool for both short-term and long-term follow-up in cancer studies and describing the various steps involved in using the NDI, is in press.

A Working Group, appointed in September 1985 by the Director of the NCI, is developing an NCI-wide policy concerning use of the NDI. It has sought advice and information from staff within the NCI, the NIH, and the NCHS on legal and administrative issues related to privacy, confidentiality and policy implementation, and is exploring the different requirements for setting policy in intramural research, contracts, grants, and cooperative agreements.

SCREENING SECTION

The overall objectives of the Section are summarized in its functional statement:

- "Plans, conducts and analyzes independent and cooperative research studies in screening for the early detection of cancer;
- conducts methodologic research in statistics, probability and epidemiology with particular emphasis on techniques appropriate to the design, analysis, and modeling of randomized and observational studies in cancer screening and related areas;
- engages in independent and cooperative research to determine cancer natural history and risk characteristics of populations for application to the design and interpretation of early detection and related studies;
- maintains liaison with other agencies, organizations and professional societies concerned with cancer screening and related methodology in order to coordinate and optimize activities."

Studies in Cancer Screening (Z01 CN 00106-04 BB)

Data from several cancer screening studies are being collected and analyzed to gain a better understanding of the impact and consequences of such screening in various population settings. Staff are involved in design, monitoring and data analysis aspects of these studies. The results can be used by the NCI in establishing cancer control policy. These data bases also provide an opportunity for the development and testing of new techniques for data analysis. The studies fall into two main categories: randomized trials and occupational cohorts.

Randomized Trials

Three large scale randomized trials have been conducted by the NCI to evaluate screening for breast, lung, and colorectal cancer. Staff participate in the scientific, and in some cases, administrative conduct of these studies. The long term follow-up phase of the HIP breast cancer screening trial was completed 23 years after the study began. This study has demonstrated a 30 percent reduction in breast cancer mortality after 10 years as a result of screening with physical examination and mammography. The reduction diminished slightly to 25 percent at 18 years. The study has also spawned several subsidiary analyses such as lead time estimation, and served as the basis for NCI policy and studies in other countries. Analysis of the final data base will focus on the magnitude and duration of the benefit, age-specific effectiveness, and the independent contribution of each screening test. Data from the lung cancer screening trial

conducted at Johns Hopkins University, Memorial Sloan Kettering Hospital, and the Mayo Clinic were edited and prepared for analysis. Initial investigations will include assessment of incidence, staging, survival, and mortality information. The colorectal cancer screening trial at the University of Minnesota is currently in progress to evaluate the Hemocult test for blood in the stool. Staff participate in scientific consultation and ongoing data monitoring for this study.

Occupational Cohorts

Screening in two high risk occupational cohorts is under investigation. In collaboration with DCE, NCI, data from the bladder cancer screening program at the DuPont Company are being analyzed to relate disease characteristics and outcome to urine cytology and blood tests, smoking history, and exposure to benzidine and beta-naphthylamine. The tests are being evaluated as indicators of exposure, predictors of disease, and for their possible impact on disease outcome through early detection. With DCE, NCI and the National Institute of Occupational Safety and Health, current follow-up data are being collected for a study of sputum cytology screening for lung cancer among uranium miners in the western United States. The relationships among cytology classification, radiation exposure, smoking history, lung cancer, and mortality data will be analyzed.

In addition to the above projects, staff have been involved in various advisory and consultative roles during the year. Consultation was provided on sample size requirements and protocol design for a study of the sensitivity and specificity of a monoclonal antibody marker test for the early detection of ovarian cancer. Feasibility, sample size, and design considerations were also addressed for a study of barium enema as a screening test in a population of individuals at high risk for colorectal cancer. Participation continued in the screening evaluation project of the International Union Against Cancer. A workshop on screening for gastrointestinal cancer concluded that there is as yet no firm evidence that screening for colorectal cancer will result in reduced mortality, and therefore such screening cannot be recommended as public health policy. A second workshop on screening for breast cancer determined that there is conclusive evidence that screening for breast cancer can reduce mortality from the disease, with the greatest initial benefit obtained by concentrating on the 50-69 age group.

Research in Cancer Screening Methodology and Modeling (Z01 CN 00105-04 BB)

The focus of this project is the development and refinement of statistical procedures for the design and analysis of cancer screening and related studies. Statistical problems under investigation include development and comparison of data analysis methods, assessment of case-control studies for screening evaluation, and development of models of cancer screening. Each of these problem areas is common to screening and prevention trials in which the Division participates, but the methods for screening studies must address the special lead time and length biases inherent in screening programs.

Lead Time and Length Bias

Research into methods to estimate and adjust for lead time and length bias have continued. Survival data in breast cancer screening are being analyzed to

attempt to isolate lead time, length and selection bias components and the relative role each plays in creating a spurious screening effect. A method to adjust survival data of screen detected cases for lead time has been developed under the assumption of independence between lead time and survival time. Extensions to the correlated situation are being pursued.

Allocating Resources in Prevention Trials

Because prevention trials and the adoption of prevention measures are expensive and resources are limited, costs and benefits need to be considered in the choice of sample size and planned accrual pattern. Previous efforts have proposed cost-effectiveness formulations for calculating sample size in simple trials with dichotomous endpoint. This research generalizes these formulations to more complex trials with a survival endpoint. In these trials, the recommendation for adoption requires both a statistically significant test of projected benefits and a prediction of cost-effectiveness at time of recommendation. If a recommendation is made, the prevention is adopted at a time-varying rate which depends on perceived benefits. Hazards for mortality are piecewise constant, and the distribution of mortality over time depends on the prevention, competing risks, and demographics.

Models for Cancer Screening Studies

Two modeling efforts are in progress. In the first, by assuming that disease progression as revealed by screening and mortality from disease following intervention depend on age but not birth cohort, and inviting a random sample of individuals by age for screening, two innovations are made possible: (1) a trial can be designed to estimate survival associated with screening patterns which may differ from those in the trial, and (2) inferences can sometimes be made from the results of a trial in which all individuals in the trial are invited for the screening. The methodology extends the model of Louis, et al (Mathematical Biosciences, 1978) to the case of periodic screens with mortality endpoint. A theorem indicates if the survival curve associated with a particular screening pattern has a unique MLE based on data generated by a given trial design.

In a second effort, creation of a screening model for colorectal cancer has been initiated. The model must account for two potential sources of benefit from screening with sigmoidoscopy or an occult blood test. One is the early detection of cancer which might result in improved survival for such individuals. The second is the detection and removal of polyps which could lead to reduced incidence and thereby reduced mortality from colorectal cancer. Initial efforts are focused on the computer simulation models of Knox and Parkin.

Case-Control Studies

In recent years, case-control methodology has been suggested for evaluating screening programs and a few studies using such methods have been carried out for cervical and breast cancer screening. At issue are the accuracy and applicability of this design for the evaluation of screening programs. Research to examine case-control studies within randomized trials of screening is underway. Estimates of the screening effect based on case-control methodology are being compared to those based on the randomized trial design. Alternative definitions of cases, controls, and exposure will be assessed, and the impact of various

matching variables will be analyzed. Data from the HIP breast cancer screening trial are being used in this analysis.

Endpoints for Screening Evaluation

The population mortality rate is the only known unbiased endpoint for assessing the impact of cancer screening. Determination of this rate usually requires long term follow-up data. Results could be obtained sooner and at less cost if the screening effect could be measured accurately using a short term endpoint which was a valid proxy or predictor of mortality. Suggested early endpoints include case survival and shift in stage distribution, but these are known to be influenced by lead time and length biases. A more promising outcome variable is the incidence rate of advanced stage disease. This research involves a comparison of this rate and other measures with mortality. Analysis of data from the HIP breast cancer screening trial suggests that the rate of Stage III and IV cancer closely mimics the mortality rate. Data for other cancer sites will also be investigated.

BIOMETRY BRANCH STAFF

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Senior Investigator, C.O.	David L. Levin, M.D., M.S.
Mathematical Statistician	Max H. Myers, Ph.D.
Secretary	Jennifer N. Gaegler
Clerk-Typist	Varnetta A. Bush

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Section Head	Charles C. Brown, Ph.D.
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Biostatistician (IPA)	Wai-yuan Tan, Ph.D.
Senior Staff Fellow	Douglas L. Weed, M.D., Ph.D.
Secretary	Caroline A. Ball

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Secretary	Julie M. Paolella

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Secretary	Gayle Marwine

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Appendix A

Intramural Project Summaries (Forms PHS 6040)

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CN 00100-04 CPSB

PERIOD COVERED

October 1, 1985 - September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

U.S.-Finland Studies of Nutrition and Cancer

PRINCIPAL INVESTIGATOR *(List other professionel personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	D.A. Albanes, M.D.	Staff Fellow	CPSB, DCPC, NCI
Others:	P.R. Taylor, M.D.	Act. Dep. Br. Chief	CPSB, DCPC, NCI
	B.K. Edwards, Ph.D.	Biostatistician	SORB, DCPC, NCI
	A.M. Hartman, M.S.	Health Statistician	SORB, DCPC, NCI

COOPERATING UNITS *(if any)*

National Public Health Institute, Helsinki, Finland
Surveillance and Operations Research Branch, DCPC

LAB/BRANCH

Cancer Prevention Studies Branch, DCPC

SECTION

INSTITUTE AND LOCATION

National Cancer Institute, NIH, Bethesda, Maryland

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.0	1.75	0.25

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The important relationship of diet and nutrition in the development of cancer has become well known through various research efforts. Laboratory studies have shown cancer inhibitory function for various natural and synthetic nutrients in various models, which have been corroborated by human epidemiologic studies of nutrient intake, tissue levels, and cancer incidence. Vitamin A, beta-carotene, and selenium have been strongly implicated for their cancer preventive potential, with sufficient evidence for these substances to warrant their use in prevention trials. In addition, the roles of other nutrients in cancer cause and prevention (e.g., dietary fats and fiber) require further investigation.

The objectives of this cooperative project with the government of Finland are: (1) to determine if either beta-carotene or alpha-tocopherol supplement is effective in preventing lung cancer in smokers; (2) to better assess the role of fats, selenium, and vitamins A, E, and C in breast cancer developement; and (3) to evaluate the relation of intake of various nutrients to subsequent cancer.
The project includes three studies. The first is a 5-year, randomized, double-blind, placebo-controlled, 2x2 factorial prevention trial of daily beta-carotene (20 mg daily) and alpha-tocopherol (50 mg daily) among smokers at high risk for lung cancer. The difference in lung cancer incidence between intervention groups will be determined. The second is a breast cancer case-control study of fats, total calories, selenium, and vitamins A, E, and C. The role of various anthropometric measurements as well as genetic markers for breast cancer will be explored. The third project will be a comparison of nutrient intakes in cases and reference subjects identified from an existing large cohort with prediagnostic baseline dietary histories. Associations between various dietary components and several cancers will be assessed. Several pilot studies have been completed to date, and the prevention trial and breast cancer study are underway.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CN 00101-04 CPSB

PERIOD COVERED

October 1, 1985 - September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Human Studies of Diet and Nutrition

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	P.R. Taylor, M.D.	Act. Dep. Br. Chief	CPSB, DCPC, NCI
	D.Y. Jones, Ph.D.	Staff Fellow	CPSB, DCPC, NCI
	M.S. Micozzi, M.D., M.S.	Staff Fellow	CPSB, DCPC, NCI
	A.G. Schatzkin, M.D., Dr.P.H.	Staff Fellow	CPSB, DCPC, NCI
	Christine A. Swanson, Ph.D., M.P.H.	Staff Fellow	CPSB, DCPC, NCI
	Elaine Lanza, Ph.D.	Senior Investigator	DCB, DCPC, NCI
Others:	B.H. Patterson, M.S.	Math. Statistician	BB, DCPC, NCI
	B.K. Edwards, Ph.D.	Biostatistician	SORB, DCPC, NCI

COOPERATING UNITS *(if any)*

U.S. Department of Agriculture, Beltsville, Human Nutrition Research Center, Surveillance and Operations Research Branch, DCPC
Biometry Branch, DCPC

LAB/BRANCH

Cancer Prevention Studies Branch, DCPC

SECTION

INSTITUTE AND LOCATION

National Cancer Institute, NIH, Bethesda, Maryland

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.0	2.25	0.75

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the spece provided.)*

The role of dietary factors in cancer prevention has been assessed in animal experiments, in human epidemiologic studies, and, most recently, in prevention trials. For many of these agents, however, information is incomplete concerning their safety, toxicity, dose, form, bioavailability, pharmacokinetics, and mechanism of action. To further define these parameters in humans, a cooperative research effort between the Beltsville Human Nutrition Research Center (BHNRC), U.S. Department of Agriculture, and the CPSB, DCPC, is being conducted. The overall goal of this collaborative effort is to obtain further information on potential cancer preventive agents. Initial efforts have focused on 3 nutrients which have shown the most promise for cancer prevention -- selenium, fat, and beta-carotene.

A study of the kinetics of a single, oral dose of two forms of selenium in the fasting and non-fasting state was conducted in the first year. Future activities will evaluate the safety/toxicity of selenium and form of ingestion among persons residing in seleniferous areas.

Our first study of fat focused on potential mechanisms of action and will assist us in the evaluation of the relation of type and amount of dietary fat to hormonal status, bile acid metabolism, and fecal mutagenic active in premenopausal women. Subsequent evaluations will examine the relation of dietary fat and fiber to fecal mutagens in men, focusing on the prominent mutagen, fecapentaene.

Beta-carotene studies are examining the plasma carotenoid response to single- and long-term ingestion of beta-carotene from either a capsule or from selected vegetables.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

ZN CN 00103-04 CPSB

PERIOD COVERED

October 1, 1985 - September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Use of Isotretinoin in Prevention of Basal Cell Carcinoma

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigetor.) (Name, title, leboratory, and institute affiliation)*

PI:	J.A. Tangrea, M.P.H.	Pharm. Res. Coord.	CPSB, DCPC, NCI
Others:	P.R. Taylor, M.D.	Act. Dep. Br. Chief	CPSB, DCPC, NCI
	B.K. Edwards, Ph.D.	Biostatistician	SORB, DCPC, NCI
	A.M. Hartman, M.S.	Health Statistician	SORB, DCPC, NCI

COOPERATING UNITS *(if any)*

Walter Reed Army Medical Center, Fitzsimons Army Medical Center, Brooke Army Medical Center, Eisenhower Army Medical Center, Portsmouth Naval Medical Center, Northwestern University, University of Arkansas, Roswell Park Medical Institute, Dermatology Branch, NCI Radiology Department Clinical Center, Surveillance and Operations Branch, DCPC

LAB/BRANCH

Cancer Prevention Studies Branch, DCPC

SECTION

INSTITUTE AND LOCATION

National Cancer Institute, NIH, Bethesda, Maryland

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
4.0	3.25	0.75

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The study is a 5-year, randomized, double-blind clinical trial designed to evaluate the effectiveness of low dosage levels of isotretinoin in reducing the incidence of basal cell carcinoma in a high-risk population, and to examine possible side effects associated with long-term administration of low doses of isotretinoin. Approximately 1,200 evaluable subjects will be entered into the study within 18 months at 8 participating clinical centers located around the country. At each center, subjects will be randomly allocated to intervention (10 mg/day) or control (placebo) groups.

The rationale for this study includes the following. Laboratory experiments have shown that retinoids administered to animals can prevent chemical carcinogenesis. In the experimental animals, retinoids were effective even if administered after exposure to the carcinogen, and therefore the prophylactic effect of the retinoids is believed to be in the postinitiation phase, i.e., during the promotion phase of carcinogenesis. Recent case reports have shown that isotretinoin can prevent the appearance of new basal cell carcinomas for four years in patients at higher risk of developing new tumors.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CN 00104-04 CPSB

PERIOD COVERED
October 1, 1985 - September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
NHANES I Epidemiologic Followup Survey: Chemoprevention/Nutrition Aspects

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	P.R. Taylor, M.D.	Act. Dep. Br. Chief	CPSB, DCPC, NCI
	G. Block, Ph.D.	Staff Fellow	SORB, DCPC, NCI
	D.Y. Jones, Ph.D.	Staff Fellow	CPSB, DCPC, NCI

Others: This research is being developed as a collaborative effort by NCHS and various institutes at NIH.

COOPERATING UNITS *(if eny)*
Biometry Branch, DCPC
NCI, NIA, NIMH, NIAAA, NHLBI, NINCDS, NIADDK, NIAID
National Center for Health Statistics

LAB/BRANCH
Cancer Prevention Studies Branch, DCPC

SECTION

INSTITUTE AND LOCATION
National Cancer Institute, NIH, Bethesda, Maryland

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.75	0.75	0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The purpose of the NHANES (National Health and Nutrition Examination Survey) Initial Epidemiologic Followup Survey was to conduct a longitudinal study of 14,407 adults originally surveyed in 1971-1975, to investigate subsequent health and mortality outcomes. Respondents have been traced and re-examined. Additional information was obtained from hosptial records, the National Death Index and death certificates. The NHANES Initial Followup Survey was completed in 1984.

The purpose of this intramural project is to examine the relationship of chemopreventive and nutritional factors as well as constitutional factors to cancer in this representive population. This study provides an opportunity to examine these factors and potentially confounding or modifying factors in a prospective fashion, and to examine the effectiveness of dietary agents which are currently of great interest for cancer prevention. The relationship of baseline vitamin use, biochemical or nutritional measures, and subsequent health status will be examined. In addition, descriptive data and trends in potential risk factors or protective factors over time will be examined. A continued followup, of the elderly (those over 75 years of age) started in 1985 while the entire cohort will be followed up in 1986.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CN 00112-03 CPSB

PERIOD COVERED

October 1, 1985 - September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Nutrition Intervention Study in Esophageal Cancer in Linxian, China

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: P.R. Taylor, M.D. Act. Dep. Br. Chief CPSB, DCPC, NCI

Others: J.A. Tangrea, M.P.H. Pharm. Res. Coord. CPSB, DCPC, NCI

COOPERATING UNITS *(if any)*

Cancer Institute, Chinese Academy of Medical Sciences, Beijing, The Peoples' Republic of China
Biostatistics Branch, DCE, NCI

LAB/BRANCH

Cancer Prevention Studies Branch, DCPC

SECTION

INSTITUTE AND LOCATION

National Cancer Institute, NIH, Bethesda, Maryland

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.5	1.5	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The purpose of this project is to conduct two intervention trials using multiple vitamin-mineral supplements to evaluate the relationship between such supplements and esophageal cancer incidence and mortality. One trial is being conducted in patients diagnosed with esophageal dysplasia (n = 3400) and the other in the general population in a high-risk region (n = 30,000). The effect of these supplements on regression/progression of esophageal dysplasia and total cancer incidence, total cancer mortality, and total mortality will be evaluated. These two studies are being conducted in Linxian (Henan Province) in the Peoples' Republic of China (PRC). Linxian, a rural country with a population of 800,000, was selected because it has the highest rate of esophageal cancer in the world (>100/100,000) and because there is suspicion that the population's chronic deficiences of multiple nutrients may be etiologically involved.

This study is being conducted jointly by the Biostatistics Branch of the Division of Cancer Etiology and the Cancer Prevention Studies Branch of the Division of Cancer Prevention and Control at the NCI in collaboration with the Cancer Institute of the Chinese Academy of Medical Sciences.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CN 00143-02 CPSB

PERIOD COVERED

October 1, 1985 - September 30, 1986

TITLE OF PROJECT *(80 charecters or less. Title must fit on one line between the borders.)*

Data from the BCDDP Project

PRINCIPAL INVESTIGATOR *(List other professionel personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	C. Carter, Ph.D., M.P.H.	Staff Fellow	CPSB, DCPC, NCI
Others:	M.S. Micozzi, M.D., M.S.	Staff Fellow	CPSB, DCPC, NCI
	A.G. Schatzkin, M.D., Dr.P.H	Staff Fellow	CPSB, DCPC, NCI
	P.R. Taylor, M.D.	Act. Dep. Br. Chief	CPSB, DCPC, NCI

COOPERATING UNITS *(if eny)*

Biometry Branch, DCPC
Environmental Epidemiology Branch, DCE

LAB/BRANCH

Cancer Prevention Studies Branch, DCPC

SECTION

INSTITUTE AND LOCATION

National Cancer Institute, NIH, Bethesda, Maryland

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.25	0.25	0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the spece provided.)*

The BCDDP screening program began in 1973 in 29 centers in 27 widely dispersed geographic areas of the United States. Initial screening was complete on over 280,000 women over a 2-year period. From the original 280,000 participants in the screening phase of the BCDDP, approximately 64,000 were selected for 5 years of long-term followup (LTF) beginning in 1978, to assess the biology and natural history of breast disease, and to test hypotheses relating to detection, etiology, and survival. Those selected for LTF included all breast cancer cases found during the screening phase, all benign breast cancer cases, all those recommended for biopsy, and a sample of "normals." The LTF data base will facilitate the exploration of important questions regarding the etiology and natural history of breast cancer. The size of the subcohorts and breadth of data available on them make this population unique. The large number of cases of both breast cancer and benign breast disease with histologic information available should allow particularly useful analyses of several risk factors in relation to these conditions.

The first 5 years of LTF will be completed in all centers by September 1986. Further follow-up of the LTF subcohorts is anticipated.

Administration of this project and its analysis is a joint effort within the Division of Cancer Prevention and Control by the Cancer Detection Branch, the Cancer Prevention Studies Branch, and the Biometry Branch, in collaboration with the Environmental Epidemiology Branch, Division of Cancer Etiology.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CN 00144-02 CPSB

PERIOD COVERED
October 1, 1985 - September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Lung Cancer Intervention Study Among Yunnan Tin Miners - Feasibility Study

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	A.G. Schatzkin, M.D., Dr.P.H.	Staff Fellow	CPSB, DCPC, NCI
Others:	J.A. Tangrea, M.P.H.	Pharm. Res. Coord.	CPSB, DCPC, NCI
	P.R. Taylor, M.D.	Act. Dep. Br. Chief	CPSB, DCPC, NCI

COOPERATING UNITS *(if any)*
Surveillance and Operations Research Branch, NCI

LAB/BRANCH
Cancer Prevention Studies Branch, DCPC

SECTION

INSTITUTE AND LOCATION
National Cancer Institute, NIH, Bethesda, Maryland

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.0	1.0	0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This pilot study will investigate the feasibility of conducting an intervention trial of micronutrients for the prevention of lung cancer among tin miners in Yunnan, China. The pilot will specifically be looking at general study logistics, ability to identify and recruit miners at high risk, adherence to pill taking, potential adverse effects from intervention agents, quality control for data and sample collection/analysis, and baseline nutritional status among the miners.

Lung cancer rates are extraordinarily high among these miners. Males > 40 years old with underground mining experience have a crude annual incidence of 1240 x 10^{-5} while miners aged 60-64 have an incidence rate in excess of 2500 x 10^{-5} annually. While the reasons for these high rates are not completely known, the miners have been exposed to a number of known carcinogens, including tobacco smoke, radon and radon daughters, and arsenic. In addition, dietary intake of several micronutrients are thought to be inadequate.

This study is being conducted by the Cancer Prevention Studies Branch in collaboration with the Department of Epidemiology of the Cancer Institute of the Chinese Academy of Medical Sciences, the Labor Protection Institute of the Yunnan Tin Corporation, and the Surveillance and Operations Research Branch.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CN-00145-01 CPSB

PERIOD COVERED

October 1, 1985 - September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Linkage of Classical and DNA Markers to the Susceptibility Gene for Breast Cancer

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: Christine Carter, Ph.D., M.P.H. Staff Fellow CPSB, DCPC, NCI

Others:

COOPERATING UNITS *(if any)*

LAB/BRANCH

Cancer Prevention Studies Branch, DCPC

SECTION

INSTITUTE AND LOCATION

National Cancer Institute, NIH, Bethesda, Maryland

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The overall goal of this project is to further an understanding of the genetic, environmental, and cultural influences that are involved in the etiology of human breast cancer. The specific aim is to test for genetic linkage between a large array of discrete, polymorphic genetic markers and the gene(s) for breast cancer in family data. The ultimate goal is to localize a gene or genes that predispose women in high-risk families to breast cancer. A sample of women with a strong family history of breast cancer who participated in the Breast Cancer Detection Demonstration Project (BCDDP) will be contacted and pedigree, vital status, health history, and epidemiological data will be collected from them and their family members. Fifteen to twenty families whose pedigree structure appears to be the most informative for use in linkage analysis studies will be selected. Blood will be collected from family members and analyzed for the presence of a number of genetic markers, including blood group antigens, red blood cell enzymes, plasma proteins, and restriction fragment length polymorphisms (RFLPs). Marker data results will then be used to perform computer generated linkage analysis.

This project is expected to start in September 1986 and continue for 3 years.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CN 00105-04 BB

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 charecters or less. Title must fit on one line between the borders.)*

Research in Cancer Screening Methodology and Modeling

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigetor.) (Name, title, laboretory, and institute affiliation)*

PI:	P. C. Prorok	Chief	SS, BB, DCPC, NCI
Others:	R. J. Connor	Mathematical Statistician	SS, BB, DCPC, NCI
	S. G. Baker	Staff Fellow	SS, BB, DCPC, NCI
	D. L. Weed	Senior Staff Fellow	BMCCES, BB, DCPC, NCI
	K. C. Chu	Health Science Administrator	CDB, PP, DCPC, NCI

COOPERATING UNITS *(if any)*

Cancer Detection Branch, Prevention Program, DCPC, NCI

LAB/BRANCH

Biometry Branch, DCPC

SECTION

Screening Section

INSTITUTE AND LOCATION

National Cancer Institute, NIH, Bethesda, Maryland 20892-4200

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.0	1.6	0.4

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

Analysis of data originally obtained from Human Subjects/Human Tissues

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the spece provided.)*

The focus of this project is development and refinement of statistical procedures for the design and analysis of cancer screening and related studies. Statistical problems under investigation include development and comparison of data analysis methods, assessment of case-control studies for screening evaluation, and development of models of cancer screening. Each of these problem areas is common to screening and prevention trials in which the Division participates, but the methods for screening studies must address the special lead time and length biases inherent in screening programs.

Properties of case-control studies in the context of screening evaluation are being considered. Screening effect as estimated from a case-control study within a randomized trial is compared with the trial result as a standard, initially using data from the HIP study. Alternative definitions of cases, controls and exposure will be assessed. An age-dependent cancer screening model that assumes no birth cohort effect and the invitation of a random sample of individuals by age to screening allows one to design a trial to estimate survival for screening patterns different from those in the trial, and to infer screening effect when all individuals undergo some screening. A computer simulation model of colorectal cancer screening is also under development. Research into short term endpoints which might be valid proxies for mortality in screening evaluation focuses on the rate of advanced stage disease. Analysis of data from the HIP study suggests the rate of Stage III and IV disease closely mimics mortality.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CN 00106-04 BB

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Studies in Cancer Screening

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	P. C. Prorok	Chief	SS, BB, DCPC, NCI
Others:	R. J. Connor	Mathematical Statistician	SS, BB, DCPC, NCI
	S. G. Baker	Staff Fellow	SS, BB, DCPC, NCI
	T. J. Mason	Chief	PSS, EEB, DCE, NCI

COOPERATING UNITS *(if any)*
PSS, Environmental Epidemiology Branch, DCE, NCI; DuPont Co. (W.Neeld), Health Ins. Plan of Greater N.Y. (W.Venet); National Inst. of Occupational Safety & Health (R.Roscoe);Internat. Union Against Ca (A.B.Miller); Centocor (V.Zuraswki)

LAB/BRANCH
Biometry Branch, DCPC

SECTION
Screening Section

INSTITUTE AND LOCATION
National Cancer Institute, NIH, Bethesda, Maryland 20892-4200

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.2	0.8	0.4

CHECK APPROPRIATE BOX(ES)
☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☒ (a1) Minors
☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Data from several cancer screening studies are being collected and analyzed to gain a better understanding of the impact and consequences of such screening in various population settings, and to develop new techniques for data analysis. Section staff are involved in various aspects of these studies, including design, monitoring and data analysis.

The long term follow-up phase of the Health Insurance Plan of New York breast cancer screening trial was completed. Current results indicate a 30 percent reduction in breast cancer mortality at 10 years, which dropped to 25 percent at 18 years. Monitoring continues of a trial to evaluate testing for blood in the stool for the early detection of colorectal cancer. Consultation was provided regarding sample size and protocol specifications for a study to assess the sensitivity and specificity of a monoclonal antibody test for the early detection of ovarian cancer.

Two occupational high risk groups are under scrutiny. In collaboration with DCE, the bladder cancer screening program at the DuPont Company is being analyzed to relate disease characteristics and outcome to urine cytology and blood tests, smoking history and chemical exposure. With DCE, and NIOSH updated follow-up data are being collected in a study of sputum cytology screening for lung cancer among uranium miners. The relationships among cytology classification, radiation exposure, smoking history, lung cancer, and mortality data will be analyzed.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CN 00107-04 BB

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 charecters or less. Title must fit on one line between the borders.)*
Design and Analysis of Pharmacokinetic Studies of Selenium

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	B. Patterson	Mathematical Statistician	CDTS, BB, DCPC, NCI
Others:	L. A. Zech	Senior Scientist	LMMB, DCBD, NCI

COOPERATING UNITS *(if any)*
Laboratory of Mathematical Biology, DCBD
Cancer Prevention Studies Branch, DCPC

LAB/BRANCH
Biometry Branch, DCPC

SECTION
Clinical and Diagnostic Trials Section

INSTITUTE AND LOCATION
National Cancer Institute, NIH, Bethesda, Maryland 20892-4200

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.5	0.4	0.1

CHECK APPROPRIATE BOX(ES)
☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Selenium is a possible cancer preventive agent, and is being considered for use in intervention trials. A study in collaboration with the Cancer Prevention Studies Branch (Z01 CN 00101-04 CPSB) is in progress which will provide information on the pharmacokinetics of selenium in its prototype forms -- sodium selenite (inorganic form) and selenomethionine (organic form). This information is unavailable for these agents in the dose currently considered optimal, and is necessary to the determination of time and manner of administration. Parameters such as percent absorption, maximum concentration, time to maximum concentration and mean residence times will be estimated for a single dose and compared in fasting and non-fasting subjects.

In order to interpret the study data more fully, development of integrated kinetic models, one for selenite and one for selenomethionine, is underway. Such models are useful in making inferences about drug metabolism and about the distribution of the drug in various body pools. A model for selenite has been developed based on pilot study data and is being tested on data from the main study. It is anticipated that the models will allow estimation of mean residence times and rates of exchange between body pools. Another aspect of the project is an analysis of variations in total selenium levels in the plasma, urine and feces both within and between individuals. This information is important in deciding what measures can be used to determine selenium status.

The Biometry Branch, in cooperation with the Cancer Prevention Studies Branch, is functioning as a data collection center, had primary responsibility for the study design, and has primary responsibility for data analysis.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CN 00113-03 BB

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Cancer in Oriental Populations

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	H. King	Research Sociologist	BMCCES, BB, DCPC, NCI
Others:	F. B. Locke	Statistician	BMCCES, BB, DCPC, NCI

COOPERATING UNITS *(if any)*

LAB/BRANCH

Biometry Branch, DCPC

SECTION

Biostatistical Methodology and Cancer Control Epidemiology Section

INSTITUTE AND LOCATION

National Cancer Institute, NIH, Bethesda, Maryland 20892-4200

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.0	1.8	0.2

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Studies of Asian Chinese represent the Division's particular interest in the ascertainment of health risk among minority populations so that appropriate interventive programs may be initiated.

- The ascertainment of health risks for Chinatown in San Francisco and New York City compared with other U.S. Chinese has been completed. Despite differences in socioeconomic characteristics between the groups, no consistent statistically significant differences in health risks were found.
- An analysis of Chinese migrants in Singapore, Taiwan and their homeland province of Fujian in the PRC is being completed. Preliminary analysis has found risks for stomach and esophageal cancer to be much lower in Taiwan and Singapore compared to Fujian.
- A third study of health risks, particularly cancer, of Chinese on Mainland China before and after 1949 is to be included as a chapter in a book on Chinese Demography.
- Analysis of incidence, mortality, and survival statistics on Chinese, Filipino, and Japanese groups in the SEER areas of San Francisco and Hawaii, and in homeland countries, continues to be updated.

Future plans include: initiation of a case-control study of lung cancer among never-smoked Chinese females in Guangzhou (China), Hong Kong, Singapore, the U.S. Bay Area, and New York City; a comparison of the mortality findings of a 65 county sub-sample on Mainland China with those of the parental PRC survey; and extension of the 1960 and 1970 U.S. studies on nativity and comparable statistics on Asian Chinese and Japanese for a two decade trend analysis.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CN 00114-03 BB

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Morbidity Among Long-Term Survivors of Childhood Cancer and Their Offspring

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	M. H. Myers	Mathematical Statistician	BB, DCPC, NCI
Others:	J. J. Mulvihill	Chief	CGS, CEB, DCE, NCI
	J. Byrne	Epidemiologist	CGS, CEB, DCE, NCI
	R. R. Connelly	Statistician	BMCCES, BB, DCPC, NCI

COOPERATING UNITS *(if any)*

Clinical Epidemiology Branch, DCE; University of Iowa; University of Kansas; University of Texas System Cancer Center; Yale University School of Medicine; California State Department of Health; ORI, Inc.; IMS, Inc.

LAB/BRANCH

Biometry Branch, DCPC

SECTION

Office of the Chief

INSTITUTE AND LOCATION

National Cancer Institute, NIH, Bethesda, Maryland 20892-4200

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.5	1.4	0.1

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This study, done in collaboration with investigators in the Division of Cancer Etiology, was designed to detect the effects of cancer and its treatment on childhood patients who survived to adulthood as well as any effects that might have been transmitted to their offspring. Specific issues for investigation were the occurrence of subsequent primary cancers, quality of life, late morbidity other than cancer and infertility among the cases and cancer and birth defects among offspring. Cases, selected from five U.S. cancer registries, had a histologically confirmed malignant neoplasm or brain tumor diagnosed under age 20 years, between 1945 and 1974, survived at least five years after diagnosis, and reached the age of 21 years. Up to two sibling controls were selected for each case with sequential priority given to full blood relationship, same sex, closest in age. Interviewer administered questionnaires were obtained for 2,285 (91%) cases and 3,265 (91%) controls.

The relative risk among married subjects (surviving cancer patients versus their sibling controls) of establishing at least one pregnancy was 0.73 (95% CL 0.69-0.79). The reduction in risk of establishing a pregnancy was in part a function of treatment of the index cancer. For surviving male patients the major risk reduction was associated with alkylating agent chemotherapy (RR=0.33, 95% CL 0.21-0.51) while for females the largest effect was due to radiation therapy (RR=0.56, 95% CL 0.43-0.73). Relative risks for combined effects of radiation plus alkylating agent chemotherapy were 0.28 for male and 0.52 for female cancer patient survivors. Thus, the combination of radiation and alkylating agents did not appreciably alter the risk when compared to the major single modality effect for each sex.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CN 00115-03 BB

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 charecters or less. Title must fit on one line between the borders.)*

Descriptive Cancer Epidemiology

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principel Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: R. R. Connelly Statistician BMCCES, BB, DCPC, NCI

COOPERATING UNITS *(if eny)*

LAB/BRANCH

Biometry Branch, DCPC

SECTION

Biostatistical Methodology and Cancer Control Epidemiology Section

INSTITUTE AND LOCATION

National Cancer Institute, NIH, Bethesda, Maryland 20892-4200

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.9	0.7	0.2

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use stenderd unreduced type. Do not exceed the space provided.)*

The primary purpose of this project is to describe and evaluate the distribution of cancer occurrence in the United States in terms of age, sex, race, place, and time in order to identify subgroups of the population that offer possibilities for mortality reduction through intervention. Cancer incidence, mortality, and survival rates are analyzed using biostatistical techniques such as log-linear models or models derived from the multistage theory of carcinogenesis. Incidence and survival data from the SEER Program and mortality data from the National Center for Health Statistics together with other data sources are often the focus of such analyses.

Trends in the incidence of mesothelioma diagnosed during 1975-84 were evaluated using age-period-cohort Poisson regression models. The average annual age-adjusted incidence rate among males increased from 5.9 to 7.6 per million population during this time. Poisson regression analysis indicated that the incidence of pleural mesothelioma peaked for the male cohort born during 1905-09.

The proportional hazards model is being used to evaluate the prognostic significance of serial antibody titers to Epstein-Barr virus antigens in treated nasopharyngeal carcinoma patients. Analyses of serial antibody titers are often complicated by censorship of the response variable and by incomplete knowledge of the patient's marker state. Both of these problems are accommodated by the proportional hazards model with titer measurements treated as a time-dependent covariate. In a series of 48 nasopharyngeal carcinoma patients who provided 288 serial serum samples, an increased risk of death was found to be significantly associated with the level of the most recent titer prior to death.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CN 00116-03 BB

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Statistical Methodology Research

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	S. B. Green	Chief	CDTS, BB, DCPC, NCI
Others:	S. Piantadosi	Medical Staff Fellow	CDTS, BB, DCPC, NCI
	D. K. Corle	Computer Systems Analyst	CDTS, BB, DCPC, NCI
	B. Patterson	Mathematical Statistician	CDTS, BB, DCPC, NCI
	P. Smith	Expert - IPA	CDTS, BB, DCPC, NCI

COOPERATING UNITS *(if any)*

Information Management Services, Inc.

LAB/BRANCH

Biometry Branch, DCPC

SECTION

Clinical and Diagnostic Trials Section

INSTITUTE AND LOCATION

National Cancer Institute, NIH, Bethesda, Maryland 20892-4200

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.9	2.4	0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The purpose of this project is to conduct research in statistical methods and computer techniques with particular emphasis on those appropriate for analyzing data from clinical, diagnostic, and prevention trials and epidemiologic studies of cancer. Many of the problems studied under this project arise from the consultative activities of the Section. During the past year, emphasis has been given to a number of projects dealing with sample size determination, including the impact of prevalent cases on prevention studies (with and without prior screening), and determination of sample sizes in the presence of arbitrary hazards. Previous work on an interactive computer program for calculating sample size was expanded to address a wider range of situations and study designs.

Another area of research has been methodology for correcting logistic regression for errors in variables (such as occur in determining dietary history). Work has continued on the analysis of cancer maps involving analysis of variations in cancer mortality. Other research has involved competing methods for analysis of qualitative interactions (where the effect of a variable is in opposite directions in different subsets). A model of the cost of clinical trials as a function of time was investigated with regard to implications for either treatment or prevention trials. Finally, work has continued on maintaining and improving software for interactive analysis of complex medical data using sophisticated multiple regression techniques and survival analysis.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CN 00119-03 BB

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 charactars or less. Title must fit on one line between the borders.)*

Consultation on Clinical Trials and Other Studies

PRINCIPAL INVESTIGATOR *(List othar profassional personnel balow the Principal Investigator.) (Nama, title, laboratory, and institute affiliation)*

PI:	S. B. Green	Chief	CDTS, BB, DCPC, NCI
Others:	S. Piantadosi	Medical Staff Fellow	CDTS, BB, DCPC, NCI
	D. K. Corle	Computer Systems Analyst	CDTS, BB, DCPC, NCI
	B. Patterson	Mathematical Statistician	CDTS, BB, DCPC, NCI
	P. Smith	Expert - IPA	CDTS, BB, DCPC, NCI

COOPERATING UNITS *(if any)*

Division of Cancer Treatment, NCI
Division of Cancer Biology and Diagnosis, NCI
Information Management Services, Inc.

LAB/BRANCH

Biometry Branch, DCPC

SECTION

Clinical and Diagnostic Trials Section

INSTITUTE AND LOCATION

National Cancer Institute, NIH, Bethesda, Maryland 20892-4200

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.7	2.3	0.4

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☒ (a1) Minors
☒ (a2) Interviews

SUMMARY OF WORK *(Usa standard unraduced type. Do not exceed the spaca provided.)*

The purpose of this project is to provide consultation on statistical and epidemiological methodology in the design, interpretation, and evaluation of clinical trials of diagnosis, treatment, and prevention of cancer, and other studies requiring this kind of expertise. For some studies the Section provides full statistical support, including development of detailed study plans, assistance in the design of appropriate study forms, supervision of randomization (for trials) and collection, processing, and editing of data, performance of interim analyses during the progress of the study, preparation of progress reports, final analysis of study data, and collaboration in the preparation of scientific papers.

During the past year the Section has continued to provide full statistical support for the randomized clinical trials of treatment conducted by the Lung Cancer Study Group and the Brain Tumor Cooperative Group. In the area of diagnosis, the Section is responsible for maintaining an up-to-date inventory and clinical data for a large serum bank containing information and sera for some 12,000 women including some with breast cancer, some with benign breast disease, and asymptomatic controls. These data are used to evaluate potential biological markers.

Some other important activities under this project include (1) multiple regression analyses of risk factors for breast cancer, using data from three major national studies; (2) studies of selenium pharmacokinetics needed for possible prevention trials; (3) a study to estimate population consumption of foods thought to be protective or harmful to cancer risk; and (4) design of a new study of food purchasing behavior and consumer nutrition information.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CN 00121-02 BB

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Research in Biostatistical Methodology and Mathematical Modeling

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	C. C. Brown	Chief	BMCCES, BB, DCPC, NCI
Others:	R. R. Connelly	Statistician	BMCCES, BB, DCPC, NCI
	W-Y. Tan	Biostatistician (IPA)	BMCCES, BB, DCPC, NCI
	Q-G. Chen	Guest Researcher	BMCCES, BB, DCPC, NCI

COOPERATING UNITS *(if any)*

Information Management Services, Inc.

LAB/BRANCH

Biometry Branch, DCPC

SECTION

Biostatistical Methodology and Cancer Control Epidemiology Section

INSTITUTE AND LOCATION

National Cancer Institute, NIH, Bethesda, Maryland 20892-4200

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.7	1.5	0.2

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The purpose of this project is research and development of biostatistical methods and mathematical models appropriate for the analysis of epidemiologic studies related to cancer control and prevention. The statistical problems being studied under this project are derived from the needs of other activities in the Division.

This research includes the development and use of mathematical models of carcinogenesis to analyze epidemiologic studies of cancer and to help predict the effects of different intervention strategies. The Armitage-Doll model has been used to quantify the effect of cigarette smoking upon early and late stages in lung cancer development; the Moolgavkar-Venzon-Knudson (MVK) two stage model is being used to quantify two hypothesized effects of a first full-term pregnancy upon breast cancer risk; the MVK model is being extended to include two different pathways to development of a malignant tumor. A mathematical model related to carcinogenesis models is being developed to predict the effect of different time-patterns of chemotherapy treatment upon a population of malignant tumor cells which is a combination of drug-sensitive and drug-resistant cells.

Research on age-period-cohort Poisson regression models is being conducted on two fronts: (1) the modeling approach has been used to disassemble the trend in lung cancer mortality into calendar period and birth cohort components; to predict the future course of lung cancer mortality in the U.S., these components have been related to past smoking behavior and the average tar content of cigarettes; and (2) a solution to the non-identifiability problem is being developed based upon use of demographic methods to decompose 5-year aggregated population age groups into single years of age. Development of a set of interactive computer programs which can be used to analyze cancer trends is also continuing.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CN 00122-02 BB

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Development of Cancer Control Epidemiologic Methods

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	D. L. Weed	Senior Staff Fellow	BMCCES, BB, DCPC, NCI
Others:	B. J. Trock	Epidemiologist	Johns Hopkins Univ.

COOPERATING UNITS *(if any)*

Johns Hopkins University

LAB/BRANCH

Biometry Branch, DCPC

SECTION

Biostatistical Methodology and Cancer Control Epidemiology Section

INSTITUTE AND LOCATION

National Cancer Institute, NIH, Bethesda, Maryland 20892-4200

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.1	0.9	0.2

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The development of the methods of cancer control epidemiology has been focused in three areas: 1) studies in causal and preventive inference, 2) studies in interactions, and 3) studies in selection bias.

One inferential issue being examined is the use of inductive and deductive logic in epidemiologic explanation. When four distinct properties of causal and preventive explanations are considered (their origin, consistency, testability, and permanence), deductive logic proves superior except for their origin which is not a logical process. The implications for cancer control epidemiology are important: competing hypotheses should be proposed before any study begins; and the choice of the best hypothesis is equivalent to that which has been most rigorously tested. Another inferential issue is that of the relationship of the current causal criteria to explanatory progress and to public health decisions. For purposes of explanation, two categories of criteria emerge: those dependent upon the form of the hypothesis being tested and those independent of it.

Studies of causal, preventive and mixed interactions have revealed that the links between biological and statistical models are necessary for scientific progress. Furthermore, the use of the multiplicative model of preventive interaction (and the use of the additive model of causal interaction) as thresholds for public health action is not justified, primarily due to ethical considerations.

Research underway includes: 1) the development of a general method to evaluate methodologic research in cancer control epidemiology, 2) a critial examination of the importance of the magnitude of an association in assessing causality, 3) further testing of a theory for the healthy worker effect, and 4) the development of the conceptual foundations of cancer control epidemiology.